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Sir:

Transmitted herewith for filing is the continuation-in-part patent application of

Inventor(s): Kenneth Rhodes, Maria Betty, Huai-Ping Ling, and Wenqian An

For: POTASSIUM CHANNEL INTERACTORS AND USES THEREFOR

Enclosed are:

☒ This is a request for filing a ☒ continuation-in-part ☐ divisional application under 37 CFR 1.53(b), of pending prior application serial no. 09/399,913, filed on September 21, 1999 entitled POTASSIUM CHANNEL INTERACTORS AND USES THEREFOR.

☒ 148 pages of specification, 14 pages of claims, 1 page of abstract.

☒ 48 sheets of formal drawings (Figures 1-43).

☒ An unexecuted Declaration, Petition and Power of Attorney.

☒ 92 pages of sequence listing (numbered 1-92).

☒ Transmittal Letter for Diskette of Sequence Listing.

☒ Diskette Containing Sequence Listing.

☒ Statement of Limited Recognition Under 37 C.F.R. §10.9(b)

The filing fee has been calculated as shown below:

	(Col. 1)	(Col. 2)
FOR:	NO. FILED	NO. EXTRA
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TOTAL CLAIMS	54-20	=34
INDEP. CLAIMS	2-3	=0
<input checked="" type="checkbox"/> MULTIPLE DEPENDENT CLAIMS PRESENTED		

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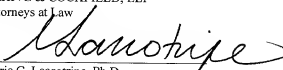
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- ☐ Any filing fees under 37 C.F.R. 1.16 for presentation of extra claims.
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- ☒ Address all future communications (May only be completed by applicant, or attorney or agent of record) to Amy E. Mandragouras at **Customer Number: 000959** whose address is:

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POTASSIUM CHANNEL INTERACTORS AND USES THEREFOR

Related Applications

- This application claims priority to U.S. provisional Application No. 60/110,033, filed on November 25, 1998, U.S. provisional Application No. 60/109,333, filed on November 20, 1998, U.S. provisional Application No. 60/110,277, filed on November 30, 1998, U.S. Patent Application No.: 09/298,731, filed on April 23, 1999, U.S. Patent Application No.: 09/350,614, filed on July 9, 1999, U.S. Patent Application No.: 09/350,874, filed on July 9, 1999, U.S. Patent Application No.: 09/399,913, filed on September 21, 1999, U.S. Patent Application No.: 09/400,492, filed on September 21, 1999, and PCT Application No. PCT/US99/27428, filed on November 19, 1999, incorporated herein in their entirety by this reference.

Background of the Invention

- Mammalian cell membranes are important to the structural integrity and activity of many cells and tissues. Of particular interest in membrane physiology is the study of trans-membrane ion channels which act to directly control a variety of pharmacological, physiological, and cellular processes. Numerous ion channels have been identified including calcium, sodium, and potassium channels, each of which have been investigated to determine their roles in vertebrate and insect cells.

- Because of their involvement in maintaining normal cellular homeostasis, much attention has been given to potassium channels. A number of these potassium channels open in response to changes in the cell membrane potential. Many voltage-gated potassium channels have been identified and characterized by their electrophysiological and pharmacological properties. Potassium currents are more diverse than sodium or calcium currents and are further involved in determining the response of a cell to external stimuli. The diversity of potassium channels and their important physiological role highlights their potential as targets for developing therapeutic agents for various diseases.

- One of the best characterized classes of potassium channels are the voltage-gated potassium channels. The prototypical member of this class is the protein encoded by the Shaker gene in *Drosophila melanogaster*. Proteins of the Shal or Kv4 family are a type of voltage-gated potassium channels that underlies many of the native A type currents that have been recorded from different primary cells. Kv4 channels have a major role in

the repolarization of cardiac action potentials. In neurons, Kv4 channels and the A currents they may comprise play an important role in modulation of firing rate, action potential initiation and in controlling dendritic responses to synaptic inputs.

The fundamental function of a neuron is to receive, conduct, and transmit signals. Despite the varied purpose of the signals carried by different classes of neurons, the form of the signal is always the same and consists of changes in the electrical potential across the plasma membrane of the neuron. The plasma membrane of a neuron contains voltage-gated cation channels, which are responsible for propagating this electrical potential (also referred to as an action potential or nerve impulse) across and along the plasma membrane.

The Kv family of channels includes, among others: (1) the delayed-rectifier potassium channels, which repolarize the membrane after each action potential to prepare the cell to fire again; and (2) the rapidly inactivating (A-type) potassium channels, which are active predominantly at subthreshold voltages and act to reduce the rate at which excitable cells reach firing threshold. In addition to being critical for action potential conduction, Kv channels also control the response to depolarizing, *e.g.*, synaptic, inputs and play a role in neurotransmitter release. As a result of these activities, voltage-gated potassium channels are key regulators of neuronal excitability (Hille B., *Ionic Channels of Excitable Membranes*, Second Edition, Sunderland, MA: Sinauer, (1992)).

There is tremendous structural and functional diversity within the Kv potassium channel superfamily. This diversity is generated both by the existence of multiple genes and by alternative splicing of RNA transcripts produced from the same gene. Nonetheless, the amino acid sequences of the known Kv potassium channels show high similarity. All appear to be comprised of four, pore forming α -subunits and some are known to have four cytoplasmic (β -subunit) polypeptides (Jan L.Y. *et al.* (1990) *Trends Neurosci* 13:415-419, and Pongs, O. *et al.* (1995) *Sem Neurosci* 7:137-146). The known Kv channel (α -subunits fall into four sub-families named for their homology to channels first isolated from *Drosophila*: the Kv1, or *Shaker*-related subfamily; the Kv2,

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or *Shab*-related subfamily; the Kv3, or *Shaw*-related subfamily; and the Kv4, or *Shal*-related subfamily.

Kv4.2 and Kv4.3 are examples of Kv channel (α -subunits of the *Shal*-related subfamily. Kv4.3 has a unique neuroanatomical distribution in that its mRNA is highly expressed in brainstem monoaminergic and forebrain cholinergic neurons, where it is involved in the release of the neurotransmitters dopamine, norepinephrine, serotonin, and acetylcholine.

This channel is also highly expressed in cortical pyramidal cells and in interneurons. (Serdio P. *et al.* (1996) *J. Neurophys* 75:2174-2179). Interestingly, the Kv4.3 polypeptide is highly expressed in neurons which express the corresponding mRNA. The Kv4.3 polypeptide is expressed in the somatodendritic membranes of these cells, where it is thought to contribute to the rapidly inactivating K⁺ conductance. Kv4.2 mRNA is widely expressed in brain, and the corresponding polypeptide also appears to be concentrated in somatodendritic membranes where it also contributes to the rapidly inactivating K⁺ conductance (Sheng *et al.* (1992) *Neuron* 9:271-84). These somatodendritic A-type Kv channels, like Kv4.2 and Kv4.3, are likely involved in processes which underlie learning and memory, such as integration of sub-threshold synaptic responses and the conductance of back-propagating action potentials (Hoffman D.A. *et al.* (1997) *Nature* 387:869-875).

Thus, proteins which interact with and modulate the activity of potassium channel proteins *e.g.*, potassium channels having a Kv4.2 or Kv4.3 subunit, provide novel molecular targets to modulate neuronal or cardiac excitability, *e.g.*, action potential conduction, somatodendritic excitability and neurotransmitter release, in cells expressing these channels. In addition, detection of genetic lesions in the gene encoding these proteins could be used to diagnose and treat central nervous system disorders such as epilepsy, spinocerebellar ataxia, anxiety, depression, age-related memory loss, migraine, obesity, Parkinsons disease or Alzheimer's disease; or cardiovascular disorders such as heart failure, hypertension, atrial fibrillation, dilated cardiomyopathy, idiopathic cardiomyopathy, or angina.

Summary of the Invention

The present invention is based, at least in part, on the discovery of novel nucleic acid molecules which encode gene products that interact with potassium channel proteins or possess substantial homology to the gene products of the invention that

5 interact with potassium channel proteins (paralogs). Potassium channel proteins are, for example, potassium channels having a Kv4.2 or Kv4.3 subunit. The nucleic acid molecules of the invention and their gene products are referred to herein as "Potassium Channel Interacting Proteins", "PCIP", or "KChIP" nucleic acid and protein molecules. The PCIP proteins of the present invention interact with, *e.g.*, bind to a potassium

10 channel protein, modulate the activity of a potassium channel protein, and/or modulate a potassium channel mediated activity in a cell, *e.g.*, a neuronal or cardiac cell. The PCIP molecules of the present invention are useful as modulating agents to regulate a variety of cellular processes, *e.g.*, neuronal or cardiac cell processes. Accordingly, in one aspect, this invention provides isolated nucleic acid molecules encoding PCIP proteins

15 or biologically active portions thereof, as well as nucleic acid fragments suitable as primers or hybridization probes for the detection of PCIP-encoding nucleic acids.

In one embodiment, a PCIP nucleic acid molecule of the invention is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more identical to the nucleotide sequence (*e.g.*, to the entire length of the nucleotide sequence) shown in SEQ

20 ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID

25 NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a complement thereof.

In another preferred embodiment, the isolated nucleic acid molecule includes the

30 nucleotide sequence shown SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ

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ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID
 NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID
 NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID
 NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID
 5 NO:71, or a complement thereof. In another preferred embodiment, the nucleic acid
 molecule includes a fragment of at least 300, 350, 400, 426, 471, or 583 nucleotides of
 the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7,
 SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ
 ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID
 10 NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID
 NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID
 NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID
 NO:71, or a complement thereof.

In another embodiment, a PCIP nucleic acid molecule includes a nucleotide
 15 sequence encoding a protein having an amino acid sequence sufficiently identical to the
 amino acid sequence of SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8,
 SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ
 ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID
 NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID
 20 NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID
 NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, or an amino acid sequence
 encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number
 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946,
 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In a preferred
 25 embodiment, a PCIP nucleic acid molecule includes a nucleotide sequence encoding a
 protein having an amino acid sequence at least 50%, 55%, 60%, 65%, 70%, 75%, 80%,
 85%, 90%, 95% or more identical to the amino acid sequence of SEQ ID NO: 2, SEQ ID
 NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14,
 SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ
 30 ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID
 NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID

NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994.

In another preferred embodiment, an isolated nucleic acid molecule encodes the amino acid sequence of 1v, 9q, p19, W28559, KChIP4a, KChIP4b, 33b07, 1p, and rat 7s protein. In yet another preferred embodiment, the nucleic acid molecule includes a nucleotide sequence encoding a protein having the amino acid sequence of SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In yet another preferred embodiment, the nucleic acid molecule is at least 426, 471, or 583 nucleotides in length and encodes a protein having a PCIP activity (as described herein).

Another embodiment of the invention features nucleic acid molecules, preferably PCIP nucleic acid molecules, which specifically detect PCIP nucleic acid molecules relative to nucleic acid molecules encoding non-PCIP proteins. For example, in one embodiment, such a nucleic acid molecule is at least 426, 400-450, 471, 450-500, 500-550, 583, 550-600, 600-650, 650-700, 700-750, 750-800 or more nucleotides in length and hybridizes under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID

NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a complement thereof. In preferred embodiments, the nucleic acid molecules are at least 15 (e.g., contiguous) nucleotides in length and hybridize under stringent conditions to nucleotides 93-126, 360-462, 732-825, 1028-1054, or 1517-1534 of SEQ ID NO:7. In other preferred embodiments, the nucleic acid molecules comprise nucleotides 93-126, 360-462, 732-825, 1028-1054, or 1517-1534 of SEQ ID NO:7.

10 In other preferred embodiments, the nucleic acid molecules are at least 15 (e.g., contiguous) nucleotides in length and hybridize under stringent conditions to nucleotides 1-14, 49-116, 137-311, 345-410, 430-482, 503-518, 662-693, 1406-1421, 1441-1457, 1478-1494, or 1882-1959 of SEQ ID NO:13. In other preferred embodiments, the nucleic acid molecules comprise nucleotides 1-14, 49-116, 137-311, 345-410, 430-482, 503-518, 662-693, 1406-1421, 1441-1457, 1478-1494, or 1882-1959 of SEQ ID NO:13.

15 In preferred embodiments, the nucleic acid molecules are at least 15 (e.g., contiguous) nucleotides in length and hybridize under stringent conditions to nucleotides 932-1527, 1548-1765, 1786-1871, 1908-2091, 2259-2265, or 2630-2654 of SEQ ID NO:35. In other preferred embodiments, the nucleic acid molecules comprise nucleotides 932-1527, 1548-1765, 1786-1871, 1908-2091, 2259-2265, or 2630-2654 of SEQ ID NO:35.

In other preferred embodiments, the nucleic acid molecule encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950,

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98951, 98991, 98993, or 98994, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 under stringent conditions.

Another embodiment of the invention provides an isolated nucleic acid molecule which is antisense to a PCIP nucleic acid molecule, *e.g.*, the coding strand of a PCIP nucleic acid molecule.

Another aspect of the invention provides a vector comprising a PCIP nucleic acid molecule. In certain embodiments, the vector is a recombinant expression vector. In another embodiment, the invention provides a host cell containing a vector of the invention. The invention also provides a method for producing a protein, preferably a PCIP protein, by culturing in a suitable medium, a host cell, *e.g.*, a mammalian host cell such as a non-human mammalian cell, of the invention containing a recombinant expression vector, such that the protein is produced.

Another aspect of this invention features isolated or recombinant PCIP proteins and polypeptides. In one embodiment, the isolated protein, preferably a PCIP protein, includes at least one calcium binding domain. In a preferred embodiment, the protein, preferably a PCIP protein, includes at least one calcium binding domain and has an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more identical to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942,

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98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In another preferred embodiment, the protein, preferably a PCIP protein, includes at least one calcium binding domain and modulates a potassium channel mediated activity. In yet another preferred embodiment, the protein, preferably a PCIP

5 protein, includes at least one calcium binding domain and is encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ

10 ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71.

In another embodiment, the invention features fragments of the proteins having

15 the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID

20 NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, wherein the fragment comprises at least 15 amino acids (*e.g.*, contiguous amino acids) of the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID

25 NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, or an amino acid sequence encoded by the DNA insert of the plasmid deposited with the ATCC as Accession

30 Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In another embodiment, the protein, preferably a PCIP protein, has the amino acid sequence of

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SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72.

In another embodiment, the invention features an isolated protein, preferably a PCIP protein, which is encoded by a nucleic acid molecule having a nucleotide sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more identical to a nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or a complement thereof.

The proteins of the present invention or biologically active portions thereof, can be operatively linked to a non-PCIP polypeptide (e.g., heterologous amino acid sequences) to form fusion proteins. The invention further features antibodies, such as monoclonal or polyclonal antibodies, that specifically bind proteins of the invention, preferably PCIP proteins. In addition, the PCIP proteins or biologically active portions thereof can be incorporated into pharmaceutical compositions, which optionally include pharmaceutically acceptable carriers.

In another aspect, the present invention provides a method for detecting the presence of a PCIP nucleic acid molecule, protein or polypeptide in a biological sample by contacting the biological sample with an agent capable of detecting a PCIP nucleic acid molecule, protein or polypeptide such that the presence of a PCIP nucleic acid molecule, protein or polypeptide is detected in the biological sample.

In another aspect, the present invention provides a method for detecting the presence of PCIP activity in a biological sample by contacting the biological sample

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with an agent capable of detecting an indicator of PCIP activity such that the presence of PCIP activity is detected in the biological sample.

In another aspect, the invention provides a method for modulating PCIP activity comprising contacting a cell capable of expressing PCIP with an agent that modulates PCIP activity such that PCIP activity in the cell is modulated. In one embodiment, the agent inhibits PCIP activity. In another embodiment, the agent stimulates PCIP activity. In one embodiment, the agent is an antibody that specifically binds to a PCIP protein. In another embodiment, the agent modulates expression of PCIP by modulating transcription of a PCIP gene or translation of a PCIP mRNA. In yet another embodiment, the agent is a nucleic acid molecule having a nucleotide sequence that is antisense to the coding strand of a PCIP mRNA or a PCIP gene.

In one embodiment, the methods of the present invention are used to treat a subject having a disorder characterized by aberrant PCIP protein or nucleic acid expression or activity by administering an agent which is a PCIP modulator to the subject. In one embodiment, the PCIP modulator is a PCIP protein. In another embodiment the PCIP modulator is a PCIP nucleic acid molecule. In yet another embodiment, the PCIP modulator is a peptide, peptidomimetic, or other small molecule. In a preferred embodiment, the disorder characterized by aberrant PCIP protein or nucleic acid expression is a CNS disorder or a cardiovascular disorder.

The present invention also provides a diagnostic assay for identifying the presence or absence of a genetic alteration characterized by at least one of (i) aberrant modification or mutation of a gene encoding a PCIP protein; (ii) mis-regulation of the gene; and (iii) aberrant post-translational modification of a PCIP protein, wherein a wild-type form of the gene encodes a protein with a PCIP activity.

In another aspect the invention provides a method for identifying a compound that binds to or modulates the activity of a PCIP protein, by providing an indicator composition comprising a PCIP protein having PCIP activity, contacting the indicator composition with a test compound, and determining the effect of the test compound on PCIP activity in the indicator composition to identify a compound that modulates the activity of a PCIP protein.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

Brief Description of the Drawings

- 5 *Figure 1* depicts the cDNA sequence and predicted amino acid sequence of human 1v. The nucleotide sequence corresponds to nucleic acids 1 to 1463 of SEQ ID NO:1. The amino acid sequence corresponds to amino acids 1 to 216 of SEQ ID NO:2.
- Figure 2* depicts the cDNA sequence and predicted amino acid sequence of rat 1v. The nucleotide sequence corresponds to nucleic acids 1 to 1856 of SEQ ID NO:3.
- 10 The amino acid sequence corresponds to amino acids 1 to 245 of SEQ ID NO:4.
- Figure 3* depicts the cDNA sequence and predicted amino acid sequence of mouse 1v. The nucleotide sequence corresponds to nucleic acids 1 to 1907 of SEQ ID NO:5. The amino acid sequence corresponds to amino acids 1 to 216 of SEQ ID NO:6.
- Figure 4* depicts the cDNA sequence and predicted amino acid sequence of rat 15 1vl. The nucleotide sequence corresponds to nucleic acids 1 to 1534 of SEQ ID NO:7. The amino acid sequence corresponds to amino acids 1 to 227 of SEQ ID NO:8.
- Figure 5* depicts the cDNA sequence and predicted amino acid sequence of mouse 1vl. The nucleotide sequence corresponds to nucleic acids 1 to 1540 of SEQ ID NO:9. The amino acid sequence corresponds to amino acids 1 to 227 of SEQ ID NO:10.
- 20 *Figure 6* depicts the cDNA sequence and predicted amino acid sequence of rat 1vn. The nucleotide sequence corresponds to nucleic acids 1 to 955 of SEQ ID NO:11. The amino acid sequence corresponds to amino acids 1 to 203 of SEQ ID NO:12.
- Figure 7* depicts the cDNA sequence and predicted amino acid sequence of human 9ql. The nucleotide sequence corresponds to nucleic acids 1 to 2009 of SEQ ID 25 NO:13. The amino acid sequence corresponds to amino acids 1 to 270 of SEQ ID NO:14.
- Figure 8* depicts the cDNA sequence and predicted amino acid sequence of rat 9ql. The nucleotide sequence corresponds to nucleic acids 1 to 1247 of SEQ ID NO:15. The amino acid sequence corresponds to amino acids 1 to 257 of SEQ ID NO:16.
- 30 *Figure 9* depicts the cDNA sequence and predicted amino acid sequence of mouse 9ql. The nucleotide sequence corresponds to nucleic acids 1 to 2343 of SEQ ID

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NO:17. The amino acid sequence corresponds to amino acids 1 to 270 of SEQ ID
NO:18.

Figure 10 depicts the cDNA sequence and predicted amino acid sequence of
human 9qm. The nucleotide sequence corresponds to nucleic acids 1 to 1955 of SEQ ID

5 NO:19. The amino acid sequence corresponds to amino acids 1 to 252 of SEQ ID
NO:20.

Figure 11 depicts the cDNA sequence and predicted amino acid sequence of rat
9qm. The nucleotide sequence corresponds to nucleic acids 1 to 2300 of SEQ ID
NO:21. The amino acid sequence corresponds to amino acids 1 to 252 of SEQ ID

10 NO:22.

Figure 12 depicts the cDNA sequence and predicted amino acid sequence of
human 9qs. The nucleotide sequence corresponds to nucleic acids 1 to 1859 of SEQ ID
NO:23. The amino acid sequence corresponds to amino acids 1 to 220 of SEQ ID
NO:24.

15 *Figure 13* depicts the cDNA sequence and predicted amino acid sequence of
monkey 9qs. The nucleotide sequence corresponds to nucleic acids 1 to 2191 of SEQ ID
NO:25. The amino acid sequence corresponds to amino acids 1 to 220 of SEQ ID
NO:26.

Figure 14 depicts the cDNA sequence and predicted amino acid sequence of rat
20 9qc. The nucleotide sequence corresponds to nucleic acids 1 to 2057 of SEQ ID NO:27.
The amino acid sequence corresponds to amino acids 1 to 252 of SEQ ID NO:28.

Figure 15 depicts the cDNA sequence and predicted amino acid sequence of rat
8t. The nucleotide sequence corresponds to nucleic acids 1 to 1904 of SEQ ID NO:29.
The amino acid sequence corresponds to amino acids 1 to 225 of SEQ ID NO:30.

25 *Figure 16* depicts the cDNA sequence and predicted amino acid sequence of
human p19. The nucleotide sequence corresponds to nucleic acids 1 to 619 of SEQ ID
NO:31. The amino acid sequence corresponds to amino acids 1 to 200 of SEQ ID
NO:32.

Figure 17 depicts the cDNA sequence and predicted amino acid sequence of rat
30 p19 The nucleotide sequence corresponds to nucleic acids 1 to 442 of SEQ ID NO:33.
The amino acid sequence corresponds to amino acids 1 to 109 of SEQ ID NO:34.

Figure 18 depicts the cDNA sequence and predicted amino acid sequence of mouse p19. The nucleotide sequence corresponds to nucleic acids 1 to 2644 of SEQ ID NO:35. The amino acid sequence corresponds to amino acids 1 to 256 of SEQ ID NO:36.

- 5 *Figure 19* depicts the cDNA sequence and predicted amino acid sequence of human W28559. The nucleotide sequence corresponds to nucleic acids 1 to 380 of SEQ ID NO:37. The amino acid sequence corresponds to amino acids 1 to 126 of SEQ ID NO:38.

- 10 *Figure 20* depicts the cDNA sequence and predicted amino acid sequence of human P193. The nucleotide sequence corresponds to nucleic acids 1 to 2176 of SEQ ID NO:39. The amino acid sequence corresponds to amino acids 1 to 41 of SEQ ID NO:40.

Figure 21 depicts a schematic representation of the rat 1v, the rat 9qm, and the mouse P19 proteins, aligned to indicate the conserved domains among these proteins.

- 15 *Figure 22* depicts the genomic DNA sequence of human 9q. *Figure 22A* depicts exon 1 and its flanking intron sequences (SEQ ID NO:46). *Figure 22B* depicts exons 2-11 and the flanking intron sequences (SEQ ID NO:47).

- 20 *Figure 23* depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4a. The nucleotide sequence corresponds to nucleic acids 1 to 2413 of SEQ ID NO:48. The amino acid sequence corresponds to amino acids 1 to 233 of SEQ ID NO:49.

- 25 *Figure 24* depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4b. The nucleotide sequence corresponds to nucleic acids 1 to 1591 of SEQ ID NO:50. The amino acid sequence corresponds to amino acids 1 to 233 of SEQ ID NO:51.

Figure 25 depicts an alignment of KChIP4a, KChIP4b, 9ql, 1v, p19, and related human paralog (hsncspara) W28559. Amino acids identical to the consensus are shaded in black, conserved amino acids are shaded in gray.

- 30 *Figure 26* depicts the cDNA sequence and predicted amino acid sequence of rat 33b07. The nucleotide sequence corresponds to nucleic acids 1 to 2051 of SEQ ID

NO:52. The amino acid sequence corresponds to amino acids 1 to 407 of SEQ ID NO:53.

Figure 27 depicts the cDNA sequence and predicted amino acid sequence of human 33b07. The nucleotide sequence corresponds to nucleic acids 1 to 4148 of SEQ ID NO:54. The amino acid sequence corresponds to amino acids 1 to 414 of SEQ ID NO:55.

Figure 28 depicts the cDNA sequence and predicted amino acid sequence of rat 1p. The nucleotide sequence corresponds to nucleic acids 1 to 2643 of SEQ ID NO:56. The amino acid sequence corresponds to amino acids 1 to 267 of SEQ ID NO:57.

Figure 29 depicts the cDNA sequence and predicted amino acid sequence of rat 7s. The nucleotide sequence corresponds to nucleic acids 1 to 2929 of SEQ ID NO:58. The amino acid sequence corresponds to amino acids 1 to 270 of SEQ ID NO:59.

Figure 30 depicts the cDNA sequence and predicted amino acid sequence of rat 29x. The nucleotide sequence corresponds to nucleic acids 1 to 1489 of SEQ ID NO:60. The amino acid sequence corresponds to amino acids 1 to 351 of SEQ ID NO:61.

Figure 31 depicts the cDNA sequence of rat 25r. The nucleotide sequence corresponds to nucleic acids 1 to 1194 of SEQ ID NO:62.

Figure 32 depicts the cDNA sequence and predicted amino acid sequence of rat 5p. The nucleotide sequence corresponds to nucleic acids 1 to 600 of SEQ ID NO:63. The amino acid sequence corresponds to amino acids 1 to 95 of SEQ ID NO:64.

Figure 33 depicts the cDNA sequence and predicted amino acid sequence of rat 7q. The nucleotide sequence corresponds to nucleic acids 1 to 639 of SEQ ID NO:65. The amino acid sequence corresponds to amino acids 1 to 212 of SEQ ID NO:66.

Figure 34 depicts the cDNA sequence and predicted amino acid sequence of rat 19r. The nucleotide sequence corresponds to nucleic acids 1 to 816 of SEQ ID NO:67. The amino acid sequence corresponds to amino acids 1 to 271 of SEQ ID NO:68.

Figure 35 depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4c. The nucleotide sequence corresponds to nucleic acids 1 to 2263 of SEQ ID NO:69. The amino acid sequence corresponds to amino acids 1 to 229 of SEQ ID NO:70.

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Figure 36 depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4d. The nucleotide sequence corresponds to nucleic acids 1 to 2259 of SEQ ID NO:71. The amino acid sequence corresponds to amino acids 1 to 250 of SEQ ID NO:72.

5 *Figure 37* depicts an alignment of KChIP4a, KChIP4b, KChIP4c, and KChIP4d.

Figure 38 depicts a graph showing the current traces from CHO cells which express Kv4.2 with or without KChIP2 (9ql). Cells are voltage clamped at -80 mV and stepped from -60 mV to +50 mV for 200ms. Peak current amplitudes at the various test voltages are shown in the right panel. *Figure 38* further depicts a table showing the
10 amplitude and kinetic effects of KChIP2 (9ql) on Kv4.2. KChIP2 expression alters the peak current amplitude, inactivation and recovery from inactivation time constants, and activation $V_{1/2}$.

Figure 39 depicts a graph showing the current traces from CHO cells which express Kv4.2 with or without KChIP3 (p19). Cells are voltage clamped at -80 mV and
15 stepped from -60 mV to +50 mV for 200ms. Peak current amplitudes at the various test voltages are shown in the right panel. *Figure 39* further depicts a table showing the amplitude and kinetic effects of KChIP3 (p19) on Kv4.2. KChIP3 causes alterations in peak current and inactivation and recovery from inactivation time constants.

Figure 40 depicts results from electrophysiological experiments demonstrating
20 that coexpression of KChIP1 dramatically alters the current density and kinetics of Kv4.2 channels expressed in CHO cells.

Figure 40A depicts current traces from a Kv4.2 transfected CHO cell. Current was evoked by depolarizing the cell sequentially from a holding potential of -80 mV to test potentials from -60 to 50 mV. Current traces are leak subtracted using a p/5
25 protocol. The current axis is shown at the same magnification as in (b) to emphasize the change in current amplitudes. Inset- Single current trace at 50mV at an expanded current axis to show the kinetics of current activation and inactivation.

Figure 40B depicts current traces as in (a), but from a cell transfected with equal amounts of DNA for Kv4.2 and KChIP1.

30 *Figure 40C* depicts peak current amplitude at all voltages from cells transfected with Kv4.2 alone (n=11) or cotransfected with KChIP1 (n=9).

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Figures 40D and 40E depict recovery from inactivation using a two pulse protocol. Kv4.2 alone (D) or coexpressed with KChIP1 (E) is driven into the inactivated state using a first pulse to 50 mV, then a second pulse to 50 mV is applied at varying times after the first pulse. Holding potential is -80 mV before and after all pulses.

- 5 *Figure 40F* depicts a summary of the percentage the peak current recovers between pulses for Kv4.2 (n=8) and Kv4.2 plus KChIP1 (n=5) transfected cells. The time constant of recovery from inactivation is fit to a single exponential.

- Figure 41* depicts an alignment of human KChIP family members with closely related members of the recoverin family of Ca²⁺ sensing proteins. (HIP:human hippocalcin; NCS1:rat neuronal calcium sensor 1). The alignment was performed using the MegAlign program for Macintosh (version 4.00 from DNASTAR) using the Clustal method with the PAM250 residue weight table and default parameters, and shaded using BOXSHADES. Residues identical to the consensus are shaded black, conservative substitutions are shaded grey. X, Y, Z and -X, -Y, -Z denote the positions of residues which are responsible for binding to the calcium ion in the EF hand.
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- 15

Figure 42 depicts a physical map of the IOSCA region.

Figure 43 depicts a linkage map showing the location of h9q and known markers associating with IOSCA and epilepsy.

20 **Detailed Description of the Invention**

- The present invention is based, at least in part, on the discovery of novel nucleic acid molecules which encode gene products that interact with potassium channel proteins or possess substantial homology to the gene products of the invention that interact with potassium channel proteins (paralogs). Potassium channel proteins are, for example, potassium channels having a Kv4.2 or Kv4.3 subunit. The nucleic acid molecules of the invention and their gene products are referred to herein as "Potassium Channel Interacting Proteins", "PCIP", or "KChIP" nucleic acid and protein molecules. Preferably, the PCIP proteins of the present invention interact with, *e.g.*, bind to a potassium channel protein, modulate the activity of a potassium channel protein, and/or modulate a potassium channel mediated activity in a cell, *e.g.*, a neuronal or cardiac cell.
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As used herein, the term "PCIP family" when referring to the protein and nucleic acid molecules of the invention is intended to mean two or more proteins or nucleic acid molecules having a PCIP activity as defined herein. Such PCIP family members can be naturally or non-naturally occurring and can be from either the same or different species.

5 For example, a PCIP family can contain a first protein of human origin, as well as other, distinct proteins of human origin or alternatively, can contain homologues of non-human origin.

As used interchangeably herein, a "PCIP activity", "biological activity of PCIP" or "functional activity of PCIP", refers to an activity exerted by a PCIP protein,

10 polypeptide or nucleic acid molecule on a PCIP responsive cell or on a PCIP protein substrate, as determined *in vivo*, or *in vitro*, according to standard techniques. In one embodiment, a PCIP activity is a direct activity, such as an association with a PCIP-target molecule. As used herein, a "target molecule" or "binding partner" is a molecule with which a PCIP protein binds or interacts in nature, such that PCIP-mediated function

15 is achieved. A PCIP target molecule can be a non-PCIP molecule or a PCIP protein or polypeptide of the present invention. In an exemplary embodiment, a PCIP target molecule is a PCIP ligand. Alternatively, a PCIP activity is an indirect activity, such as a cellular signaling activity mediated by interaction of the PCIP protein with a PCIP ligand. The biological activities of PCIP are described herein.

20 For example, the PCIP proteins of the present invention can have one or more of the following activities: (1) they can interact with (*e.g.*, bind to) a potassium channel protein or portion thereof; (2) they can regulate the phosphorylation state of a potassium channel protein or portion thereof; (3) they can associate with (*e.g.*, bind) calcium and can, for example, act as calcium dependent kinases, *e.g.*, phosphorylate a potassium

25 channel or a G-protein coupled receptor in a calcium-dependent manner; (4) they can associate with (*e.g.*, bind) calcium and can, for example, act in a calcium-dependent manner in cellular processes, *e.g.*, act as calcium dependent transcription factors; (5) they can modulate a potassium channel mediated activity in a cell (*e.g.*, a neuronal cell such as a sensory neuron cell or a motor neuron cell, or a cardiac cell) to, for example,

30 beneficially affect the cell; (6) they can modulate chromatin formation in a cell, *e.g.*, a neuronal or cardiac cell; (7) they can modulate vesicular traffic and protein transport in a

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cell, *e.g.*, a neuronal or cardiac cell; (8) they can modulate cytokine signaling in a cell, *e.g.*, a neuronal or cardiac cell; (9) they can regulate the association of a potassium channel protein or portion thereof with the cellular cytoskeleton; (10) they can modulate cellular proliferation; (11) they can modulate the release of neurotransmitters; (12) they can modulate membrane excitability; (13) they can influence the resting potential of membranes; (14) they can modulate wave forms and frequencies of action potentials; and (15) they can modulate thresholds of excitation.

As used herein, a "potassium channel" includes a protein or polypeptide that is involved in receiving, conducting, and transmitting signals in an excitable cell.

- 10 Potassium channels are typically expressed in electrically excitable cells, *e.g.*, neurons, cardiac, skeletal and smooth muscle, renal, endocrine, and egg cells, and can form heteromultimeric structures, *e.g.*, composed of pore-forming and cytoplasmic subunits. Examples of potassium channels include: (1) the voltage-gated potassium channels, (2) the ligand-gated potassium channels, and (3) the mechanically-gated potassium
- 15 channels. For a detailed description of potassium channels, see Kandel E.R. *et al.*, Principles of Neural Science, second edition, (Elsevier Science Publishing Co., Inc., N.Y. (1985)), the contents of which are incorporated herein by reference. The PCIP proteins of the present invention have been shown to interact with, for example, potassium channels having a Kv4.3 subunit or a Kv4.2 subunit.

- 20 As used herein, a "potassium channel mediated activity" includes an activity which involves a potassium channel, *e.g.*, a potassium channel in a neuronal cell or a cardiac cell, associated with receiving, conducting, and transmitting signals in, for example, the nervous system or in the heart. Potassium channel mediated activities include release of neurotransmitters, *e.g.*, dopamine or norepinephrine, from cells, *e.g.*,
- 25 neuronal or cardiac cells; modulation of resting potential of membranes, wave forms and frequencies of action potentials, and thresholds of excitation; and modulation of processes such as integration of sub-threshold synaptic responses and the conductance of back-propagating action potentials in, for example, neuronal cells or cardiac cells.

- 30 As the PCIP proteins of the present invention modulate potassium channel mediated activities, they may be useful as novel diagnostic and therapeutic agents for potassium channel associated disorders and/or nervous system related disorders.

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Moreover, the PCIP proteins of the present invention modulate Kv4 potassium channels, e.g., potassium channels having a Kv4.2 or Kv4.3 subunit, which underlie the voltage-gated K⁺ current known as I_{to} (transient outward current) in the mammalian heart (KaaB S. *et al.* (1998) *Circulation* 98(14):1383-93; Dixon J.E. *et al.* (1996) *Circulation Research* 79(4):659-68; Nerbonne JM (1998) *Journal of Neurobiology* 37(1):37-59; Barry D.M. *et al.* (1998) *Circulation Research* 83(5):560-7; Barry D.M. *et al.* (1996) *Annual Review of Physiology* 58:363-94. This current underlies the rapid repolarization of cardiac myocytes during an action potential. It also participates in the inter-beat interval by controlling the rate at which cardiac myocytes reach the threshold for firing a subsequent action potential.

This current is also known to be down regulated in patients with cardiac hypertrophy, resulting in prolongation of the cardiac action potential. In these patients, action potential prolongation is thought to produce changes in calcium load and calcium handling within the myocardium, which contributes to the progression of cardiac disease from hypertrophy to heart failure (Wickenden *et al.* (1998) *Cardiovascular Research* 37:312). Interestingly, several PCIPs of the present invention (e.g., 9ql, 9qm, 9qs, shown in SEQ ID NOs:13, 15, 17, 19, 21, 23, and 25) bind to and modulate potassium channels containing a Kv4.2 or Kv4.3 subunit and contain calcium binding EF-hand domains. Because of mutations in these PCIP genes, defects in the expression of these calcium-binding PCIP proteins themselves, or defects in the interaction between these PCIPs and Kv4.2 or Kv4.3 channels, might be expected to lead to decreases in KV4.3 or Kv4.3(I_m) currents in the myocardium, therapeutic agents that alter PCIP expression or modulate the interaction between these PCIPs and Kv4.2 or Kv4.3 may be extremely valuable agents to slow or prevent the progression of disease from hypertrophy to heart failure.

As used herein, a "potassium channel associated disorder" includes a disorder, disease or condition which is characterized by a misregulation of a potassium channel mediated activity. Potassium channel associated disorders can detrimentally affect conveyance of sensory impulses from the periphery to the brain and/or conductance of motor impulses from the brain to the periphery; integration of reflexes; interpretation of sensory impulses; and emotional, intellectual (e.g., learning and memory), or motor

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processes. Potassium channel associated disorders can further detrimentally affect electrical impulses that stimulate the cardiac muscle fibers to contract. Examples of potassium channel associated disorders include nervous system related disorders, as well as cardiovascular disorders.

- 5 As used herein, a "nervous system related disorder" includes a disorder, disease or condition which affects the nervous system. Examples of potassium channel associated disorders and nervous system related disorders include cognitive disorders, e.g., memory and learning disorders, such as amnesia, apraxia, agnosia, amnesic dysnomia, amnesic spatial disorientation, Kluver-Bucy syndrome, Alzheimer's related
- 10 memory loss (Eglen R.M. (1996) *Pharmacol. and Toxicol.* 78(2):59-68; Perry E.K. (1995) *Brain and Cognition* 28(3):240-58) and learning disability; disorders affecting consciousness, e.g., visual hallucinations, perceptual disturbances, or delirium associated with Lewy body dementia; schizo-affective disorders (Dean B. (1996) *Mol. Psychiatry* 1(1):54-8), schizophrenia with mood swings (Bymaster F.P. (1997) *J. Clin.*
- 15 *Psychiatry* 58 (suppl.10):28-36; Yeomans J.S. (1995) *Neuropharmacol.* 12(1):3-16; Reimann D. (1994) *J. Psychiatric Res.* 28(3):195-210), depressive illness (primary or secondary); affective disorders (Janowsky D.S. (1994) *Am. J. Med. Genetics* 54(4):335-44); sleep disorders (Kimura F. (1997) *J. Neurophysiol.* 77(2):709-16), e.g., REM sleep abnormalities in patients suffering from, for example, depression (Reimann D. (1994) *J.*
- 20 *Psychosomatic Res.* 38 Suppl. 1:15-25; Bourgin P. (1995) *Neuroreport* 6(3): 532-6), paradoxical sleep abnormalities (Sakai K. (1997) *Eur. J. Neuroscience* 9(3):415-23), sleep-wakefulness, and body temperature or respiratory depression abnormalities during sleep (Shuman S.L. (1995) *Am. J. Physiol.* 269(2 Pt 2):R308-17; Mallick B.N. (1997) *Brain Res.* 750(1-2):311-7). Other examples of nervous system related disorders include
- 25 disorders affecting pain generation mechanisms, e.g., pain related to irritable bowel syndrome (Mitch C.H. (1997) *J. Med. Chem.* 40(4):538-46; Shannon H.E. (1997) *J. Pharmac. and Exp. Therapeutics* 281(2):884-94; Bouaziz H. (1995) *Anesthesia and Analgesia* 80(6):1140-4; or Guimaraes A.P. (1994) *Brain Res.* 647(2):220-30) or chest pain; movement disorders (Monassi C.R. (1997) *Physiol. and Behav.* 62(1):53-9), e.g.,
- 30 Parkinson's disease related movement disorders (Finn M. (1997) *Pharmacol. Biochem. & Behavior* 57(1-2):243-9; Mayorga A.J. (1997) *Pharmacol. Biochem. & Behavior*

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- 56(2):273-9); eating disorders, *e.g.*, insulin hypersecretion related obesity (Maccario M. (1997) *J. Endocrinol. Invest.* 20(1):8-12; Premawardhana L.D. (1994) *Clin. Endocrinol.* 40(5): 617-21); drinking disorders, *e.g.*, diabetic polydipsia (Murzi E. (1997) *Brain Res.* 752(1-2):184-8; Yang X. (1994) *Pharmacol. Biochem. & Behavior* 49(1):1-6);
- 5 neurodegenerative disorders, *e.g.*, Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, spinocerebellar ataxia, epileptic syndromes, and Jakob-Creutzfeldt disease; psychiatric disorders, *e.g.*, depression, schizophrenic disorders, Korsakoff's psychosis,
- 10 mania, anxiety disorders, bipolar affective disorders, or phobic disorders; neurological disorders, *e.g.*, migraine; spinal cord injury; stroke; and head trauma.

As used herein, "epilepsy" includes a common neurological disorder caused by disturbances in the normal electrical functions of the brain. In normal brain function millions of tiny electrical charges pass from nerve cells in the brain to all parts of the body. In patients with epilepsy, this normal pattern is interrupted by sudden and unusually intense bursts of electrical energy, which may briefly affect a person's consciousness, bodily movements, or sensations. These physical changes are called epileptic seizures. There are two categories of seizures: partial seizures, which occur in one area of the brain, and generalized seizures, which affect nerve cells throughout the brain. Epilepsy may result from a brain injury before, during, or after birth; head trauma; poor nutrition; some infectious diseases; brain tumors; and some poisons. However, in many cases the cause is unknown. Attacks of epilepsy may be preceded by a feeling of unease or sensory discomfort called an aura, which indicates the beginning of the seizure. Signs of an impending epileptic seizure, which vary among patients, may include visual phenomena such as flickering lights or "sunbursts." Recently, a genetic linkage for epilepsy has been found on chromosome 10q, near marker D10S192: 10q22-q24 (Ottman et al. (1995) *Nature Genetics* 10:56-60). The many forms of epilepsy include: grand mal, Jacksonian, myoclonic progressive familial, petit mal, Lennox-Gastaut syndrome, febrile seizures, psycho-motor, and temporal lobe. The observations described herein are particularly useful in developing treatments for partial epilepsy.

As used herein, "ataxia" includes a common neurological disorder caused by disturbances in the normal electrical functions of the brain. Spinocerebellar ataxia type 1 (SCA1) is an autosomal dominant disorder which is genetically linked to the short arm of chromosome 6 based on linkage to the human major histocompatibility complex (HLA). See, for example, H. Yakura *et al.* (1974) *N. Engl. J. Med.*, 291, 154-155; and J. F. Jackson *et al.* (1977) *N. Engl. J. Med.* 296, 1138-1141. SCA1 has been shown to be tightly linked to the marker D6S89 on the short arm of chromosome 6, telomeric to HLA. See, for example, L. P. W. Ranum *et al.*, *Am. J. Hum. Genet.*, 49, 31-41 (1991); and H. Y. Zoghbi *et al.*, *Am. J. Hum. Genet.*, 49, 23-30 (1991). The observations described herein are particularly useful in developing treatments for infantile onset spinocerebellar ataxia (IOSCA).

As used herein, a "cardiovascular disorder" includes a disorder affecting the cardiovascular system, *e.g.*, the heart. Examples of cardiovascular disorders include arteriosclerosis, ischemia reperfusion injury, restenosis, arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, atrial fibrillation, long-QT syndrome, congestive heart failure, sinus node dysfunction, angina, heart failure, hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrhythmia. In a preferred embodiment, the cardiovascular disorder is associated with an abnormal I_{to} current.

Some members of a PCIP family may also have common structural characteristics, such as a common structural domain or motif or a sufficient amino acid or nucleotide sequence homology as defined herein. Such PCIP family members can be naturally or non-naturally occurring and can be from either the same or different species. For example, a PCIP family can contain a first protein of human origin, as well as other, distinct proteins of human origin or alternatively, can contain homologues of non-human origin.

For example, members of a PCIP family which have common structural characteristics, may comprise at least one "calcium binding domain". As used herein,

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the term "calcium binding domain" includes an amino acid domain, *e.g.*, an EF hand (Bainbridge K.G. *et al.* (1992) *TINS* 15(8): 303-308), which is involved in calcium binding. Preferably, a calcium binding domain has a sequence, which is substantially identical to the consensus sequence:

5

EO••OO••ODKDGDG•O••EF••OO. (SEQ ID NO:41).

O can be I, L, V or M, and "•" indicates a position with no strongly preferred residue. Each residue listed is present in more than 25% of sequences, and those underlined are present in more than 80% of sequences. Amino acid residues 126-154 and 174-202 of the human 1v protein, amino acid residues 126-154 and 174-202 of the rat 1v protein, amino acid residues 137-165 and 185-213 of the rat 1vl protein, amino acid residues 142-170 of the rat 1vn protein, amino acid residues 126-154 and 174-202 of the mouse 1v protein, amino acid residues 137-165 and 185-213 of the mouse 1vl protein, amino acid residues 144-172, 180-208, and 228-256 of the human 9q1 protein, amino acid residues 126-154, 162-190, and 210-238 of the human 9qm protein, amino acid residues 94-122, 130-158, and 178-206 of the human 9qs protein, amino acid residues 126-154, 162-190, and 210-238 of the rat 9qm protein, amino acid residues 131-159, 167-195, and 215-243 of the rat 9ql protein, amino acid residues 126-154, 162-190, and 210-238 of the rat 9qc protein, amino acid residues 99-127, 135-163, and 183-211 of the rat 8t protein, amino acid residues 144-172, 180-208, and 228-256 of the mouse 9ql protein, amino acid residues 94-122, 130-158, and 178-206 of the monkey 9qs protein, amino acid residues 94-122, 130-158, and 178-206 of the human p19 protein, amino acid residues 19-47 and 67-95 of the rat p19 protein, and amino acid residues 130-158, 166-194, and 214-242 of the mouse p19 protein comprise calcium binding domains (EF hands) (see Figure 21). Amino acid residues 116-127 and 152-163 of the monkey KChIP4a and KChIP4b proteins comprise calcium binding domains.

In another embodiment, the isolated PCIP proteins of the present invention are identified based on the presence of at least one conserved carboxyl-terminal domain which includes an amino acid sequence of about 100-200 amino acid residues in length, preferably 150-200 amino acid residues in length, and more preferably 185 amino acid

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residues in length, and which includes three EF hands. PCIP proteins of the present invention preferably contain a carboxyl-terminal domain which is at least about 70%, 71%, 74%, 75%, 76%, 80%, or more identical to the carboxyl terminal 185 amino acid residues of rat 1v, rat 9q, or mouse p19 (see Figures 21, 25, and 41).

5 Members of the PCIP family which also have common structural characteristics are listed in Table I and described below. The invention provides full length human, mouse, and rat 1v cDNA clones, full length mouse and rat cDNA clones of 1v splice variant 1vl, a partial rat cDNA clone of 1v splice variant 1vn, and the proteins encoded by these cDNAs. The invention further provides full length human and mouse and
10 partial rat 9ql cDNA clones, full length human and rat cDNA clones of 9ql splice variant 9qm, full length human and monkey cDNA clones of 9ql splice variant 9qs, a full length rat cDNA clone of 9ql splice variant 9qc, a partial rat cDNA clone of 9ql splice variant 8t, and the proteins encoded by these cDNAs. The invention also provides full length mouse and human and partial rat p19 cDNA clones and the proteins encoded by these
15 cDNAs. A full length human cDNA clone of p19 is provided, and a partial clone p193, representing the 3' end of the human p19 cDNA. In addition, the invention provides a partial human W28559 cDNA clone and the protein encoded by this cDNA. The invention further provides a full length monkey clone, KChIP4a, and a corresponding full length splice variant, KChIP4b and the proteins encoded by these cDNAs.

20 Other members of the PCIP family, *e.g.*, members of the PCIP family which do not have common structural characteristics, are listed in Table II and are described below. The present invention provides a full length human and a partial length rat 33b07 clone and the proteins encoded by these cDNAs. The present invention further provides partial length rat 1p clone and the protein encoded by this cDNA. In addition,
25 the present invention provides a partial length rat 7s clone and the protein encoded by this cDNA.

 The present invention further provides PCIP family members which represent previously identified cDNAs (29x, 25r, 5p, 7q, and 19r). These previously identified cDNAs are identified herein as PCIP family members, *i.e.*, as molecules which have a
30 PCIP activity, as described herein. Accordingly, the present invention provides methods for using these previously identified cDNAs, *e.g.*, methods for using these cDNAs in the

screening assays, the diagnostic assays, the prognostic assays, and the methods of treatment described herein.

The PCIP molecules of the present invention were initially identified based on their ability, as determined using yeast two-hybrid assays (described in detail in Example 1), to interact with the amino-terminal 180 amino acids of rat Kv4.3 subunit. Further binding studies with other potassium subunits were performed to demonstrate specificity of the PCIP for Kv4.3 and Kv4.2. *In situ* localization, immuno-histochemical methods, co-immunoprecipitation and patch clamping methods were then used to clearly demonstrate that the PCIPs of the present invention interact with and modulate the activity of potassium channels, particularly those comprising a 4.3 or 4.2 subunit.

Several novel human, mouse, monkey, and rat PCIP family members have been identified, referred to herein as 1v, 9q, p19, W28559, KChIP4, 33b07, 1p, and rat 7s proteins and nucleic acid molecules. The human, rat, and mouse cDNAs encoding the 1v polypeptide are represented by SEQ ID NOs: 1, 3, and 5, and shown in Figures 1, 2, and 3, respectively. In the brain, 1v mRNA is highly expressed in neocortical and hippocampal interneurons, in the thalamic reticular nucleus and medial habenula, in basal forebrain and striatal cholinergic neurons, in the superior colliculus, and in cerebellar granule cells. The 1v polypeptide is highly expressed in the somata, dendrites, axons and axon terminals of cells that express 1v mRNA. Splice variants of the 1v gene have been identified in rat and mouse and are represented by SEQ ID NOs: 7, 9, and 11 and shown in Figures 4, 5, and 6, respectively. 1v polypeptide interacts with potassium channels comprising Kv4.3 or kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot, the 1v transcripts (mRNA) are expressed predominantly in the brain

The 8t cDNA (SEQ ID NO: 29) encodes a polypeptide having a molecular weight of approximately 26 kD corresponding to SEQ ID NO:30 (see Figure 15). The 8t polypeptide interacts with potassium channel comprising Kv4.3 or Kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot and *in situ* data, the 8t mRNA is expressed predominantly in the heart and the brain. The 8t cDNA is a splice variant of 9q.

Human, rat, monkey, and mouse 9q cDNA were also isolated. Splice variants include human 9ql (SEQ ID NO:13; Figure 7) rat 9ql (SEQ ID NO:15; Figure 8), mouse 9ql (SEQ ID NO:17; Figure 9), human 9qm (SEQ ID NO:19; Figure 10), rat 9qm (SEQ ID NO:21; Figure 11), human 9qs (SEQ ID NO:23; Figure 12), monkey 9qs (SEQ ID NO:25; Figure 13), and rat 9qc (SEQ ID NO:27; Figure 14). The genomic DNA sequence of 9q has also be determined. Exon 1 and its flanking intron sequences (SEQ ID NO:46) are shown in Figure 22A. Exons 2-11 and the flanking intron sequences (SEQ ID NO:47) are shown in Figure 22B. 9q polypeptides interact with potassium channels comprising Kv4.3 or Kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot and *in situ* data, the 9q proteins are expressed predominantly in the heart and the brain. In the brain, 9q mRNA is highly expressed in the neostriatum, hippocampal formation, neocortical pyramidal cells and interneurons, and in the thalamus, superior colliculus, and cerebellum.

Human, rat, and mouse P19 cDNA was also isolated. Human P19 is shown in SEQ ID NO:31 and Figure 16; and in SEQ ID NO:39 and Figure 20 (the 3' sequence). Rat P19 is shown in SEQ ID NO:33 and Figure 17, and mouse P19 is shown in SEQ ID NO:35 and Figure 18. P19 polypeptides interact with potassium channels comprising Kv4.3 or Kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot analysis, the P19 transcripts (mRNA) are expressed predominantly in the brain.

A partial human paralog of the PCIP molecules was also identified. This paralog is referred to herein as W28559 and is shown in SEQ ID NO:37 and Figure 19.

Monkey KChIP4a and its splice variants KChIP4b, KChIP4c, and KChIP4d were also identified. Monkey KChIP4a is shown in SEQ ID NO:48 and Figure 23. Monkey KChIP4b is shown in SEQ ID NO:50 and Figure 24. Monkey KChIP4c is shown in SEQ ID NO:69 and Figure 35. Monkey KChIP4d is shown in SEQ ID NO:71 and Figure 36.

The nucleotide sequence of the full length rat 33b07 cDNA and the predicted amino acid sequence of the rat 33b07 polypeptide are shown in Figure 26 and in SEQ ID NOs:52 and 53, respectively. The rat 33b07 cDNA encodes a protein having a molecular weight of approximately 44.7 kD and which is 407 amino acid residues in

length. Rat 33b07 binds rKv4.3N and rKv4.2N with slight preference for rKv4.2N in yeast 2-hybrid assays.

The nucleotide sequence of the full length human 33b07 cDNA and the predicted amino acid sequence of the human 33b07 polypeptide are shown in Figure 27 and in SEQ ID NOs:54 and 55, respectively.

The nucleotide sequence of the partial length rat 1p cDNA and the predicted amino acid sequence of the rat 1p polypeptide are shown in Figure 28 and in SEQ ID NOs:56 and 57, respectively. The rat 1p cDNA encodes a protein having a molecular weight of approximately 28.6 kD and which is 267 amino acid residues in length. Rat 1p binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast two-hybrid assays.

The nucleotide sequence of the partial length rat 7s cDNA and the predicted amino acid sequence of the rat 7s polypeptide are shown in Figure 29 and in SEQ ID NOs:58 and 59, respectively. The rat 7s cDNA encodes a protein having a molecular weight of approximately 28.6 kD and which is 270 amino acid residues in length. Rat 7s binds rKv4.3N and rKv4.2N with preference for rKv4.3N in yeast two-hybrid assays.

The sequences of the present invention are summarized below, in Tables I and II.

Table I

Novel Polynucleotides and Polypeptides of the Present Invention (full length except where noted)

PCIP	Nucleic Acid Molecule Form	Source	SEQ ID NO: DNA	SEQ ID NO: PROTEIN	ATCC
1v or KChIP1	1v	human (225-875)*	1	2	98994
	1v	rat (210-860)	3	4	98946

	lv	mouse (477-1127)	5	6	98945
	lvI	rat (31-714)	7	8	98942
	lvI	mouse (77-760)	9	10	98943
	lvn (partial)	rat (345-955)	11	12	98944
9q or KChIP2	Genomic DNA sequence (Exon 1 and flanking intron sequences)	human	46		
	Genomic DNA sequence (Exons 2-11 and flanking intron sequences)	human	47		
	9qI	human (207-1019)	13	14	98993 98991
	9qI (partial)	rat (2-775)	15	16	98948
	9qI	mouse (181 -993)	17	18	98937
	9qm	human (207-965)	19	20	98993 98991
	9qm	rat (214-972)	21	22	98941

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	9qs	human (207-869)	23	24	98951
	9qs	monkey (133-795)	25	26	98950
	9qc	rat (208-966)	27	28	98947
	8t (partial)	rat (1-678)	29	30	98939
p19 or KChIP3	p19	Human (1-771)	31	32	PTA-316
	p19 (partial)	rat (1-330)	33	34	98936
	p19	mouse (49-819)	35	36	98940
	p193 (partial)	Human (2-127)	39	40	98949
W28559	W28559 (partial)	human (1-339)	37	38	
KChIP4	KChIP4a	Monkey (265-966)	48	49	
	KChIP4b C-terminal splice variant	Monkey (265-966)	50	51	
	KChIP4c splice variant	Monkey (122-811)	69	70	
	KChIP4d splice variant	Monkey (64-816)	71	72	

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* The coordinates of the coding sequence are shown in parenthesis. The first column indicates the PCIPs which were identified and column 2 indicates the various nucleic acid forms identified for each PCIP.

5 Table II

Polynucleotides and Polypeptides of the Present Invention (full length except where noted)

PCIP	Nucleic Acid Molecule Form	Source	SEQ ID NO: DNA	SEQ ID NO: PROTEIN	ATCC
33b07 Novel	33b07	Human (88-1332)	52	53	PTA-316
	33b07	Rat (85-1308)	54	55	
1p Novel	1p (partial)	Rat (1-804)	56	57	
7s Novel	7s (partial)	Rat (1-813)	58	59	
29x	29x	Rat (433-1071)	60	61	
	25r splice variant of 29x	Rat (130-768)	62		
5p	5p	Rat (52-339)	63	64	
7q	7q	Rat (1-639)	65	66	
19r	19r	Rat (1-816)	67	68	

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* The coordinates of the coding sequence are shown in parenthesis. The first column indicates the four families of PCIPs which were identified and column 2 indicates the various nucleic acid forms identified for each family. Novel molecules are also indicated.

- 5 Plasmids containing the nucleotide sequences encoding human, rat and monkey PCIPs were deposited with American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, on November 17, 1998, and assigned the Accession Numbers described above. These deposits will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of
- 10 Microorganisms for the Purposes of Patent Procedure. These deposits were made merely as a convenience for those of skill in the art and are not an admission that a deposit is required under 35 U.S.C. §112.

- Clones containing cDNA molecules encoding human p19 (clone EphP19) and human 33b07 (clone Eph33b07) were deposited with American Type Culture Collection
- 15 (Manassas, VA) on July 8, 1998 as Accession Number PTA-316, as part of a composite deposit representing a mixture of two strains, each carrying one recombinant plasmid harboring a particular cDNA clone. (The ATCC strain designation for the mixture of hP19 and h33b07 is EphP19h33b07mix).

- To distinguish the strains and isolate a strain harboring a particular cDNA clone,
- 20 an aliquot of the mixture can be streaked out to single colonies on LB plates supplemented with 100 ug/ml ampicillin, single colonies grown, and then plasmid DNA extracted using a standard miniprep procedure. Next, a sample of the DNA miniprep can be digested with NotI and the resultant products resolved on a 0.8% agarose gel using standard DNA electrophoresis conditions. The digest gives the
- 25 following band patterns: EphP19: 7 kb 9 (single band), Eph33b07: 5.8 kb (single band).

Various aspects of the invention are described in further detail in the following subsections:

I. Isolated Nucleic Acid Molecules

One aspect of the invention pertains to isolated nucleic acid molecules that encode PCIP proteins or biologically active portions thereof, as well as nucleic acid fragments sufficient for use as hybridization probes to identify PCIP-encoding nucleic acid molecules (e.g., PCIP mRNA) and fragments for use as PCR primers for the amplification or mutation of PCIP nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (e.g., cDNA or genomic DNA) and RNA molecules (e.g., mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid. Preferably, an "isolated" nucleic acid is free of sequences which naturally flank the nucleic acid (i.e., sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated PCIP nucleic acid molecule can contain less than about 5 kb, 4kb, 3kb, 2kb, 1 kb, 0.5 kb or 0.1 kb of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the present invention, e.g., a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with

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ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a portion thereof, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or portion of the nucleic acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, as a hybridization probe, PCIP nucleic acid molecules can be isolated using standard hybridization and cloning techniques (e.g., as described in Sambrook, J., Fritsch, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual*. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

Moreover, a nucleic acid molecule encompassing all or a portion of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994 can be isolated by the polymerase chain reaction (PCR) using synthetic oligonucleotide primers designed based upon the sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ

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ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID
 NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID
 NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID
 NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the

- 5 nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as
 Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944,
 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994.

- A nucleic acid of the invention can be amplified using cDNA, mRNA or
 alternatively, genomic DNA, as a template and appropriate oligonucleotide primers
 10 according to standard PCR amplification techniques. The nucleic acid so amplified can
 be cloned into an appropriate vector and characterized by DNA sequence analysis.
 Furthermore, oligonucleotides corresponding to PCIP nucleotide sequences can be
 prepared by standard synthetic techniques, e.g., using an automated DNA synthesizer.

- In a preferred embodiment, an isolated nucleic acid molecule of the invention
 15 comprises the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID
 NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15,
 SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ
 ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID
 NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID
 20 NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID
 NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid
 deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940,
 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951,
 98991, 98993, or 98994, or a portion of any of these nucleotide sequences.

- 25 In another preferred embodiment, an isolated nucleic acid molecule of the
 invention comprises a nucleic acid molecule which is a complement of the nucleotide
 sequence shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID
 NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID
 NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID
 30 NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID
 NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID

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NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a portion of any of these nucleotide sequences. A nucleic acid molecule which is complementary to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, is one which is sufficiently complementary to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, such that it can hybridize to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, thereby forming a stable duplex.

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- In still another preferred embodiment, an isolated nucleic acid molecule of the present invention comprises a nucleotide sequence which is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more identical to the entire length of the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the entire length of the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a portion of any of these nucleotide sequences.
- Moreover, the nucleic acid molecule of the invention can comprise only a portion of the nucleic acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, for example a fragment which can be used as a probe or primer or a fragment encoding a biologically active portion of a PCIP protein. The nucleotide sequence determined from the cloning of the PCIP gene allows for the generation of probes and primers designed for use in identifying and/or cloning other PCIP family members, as well as PCIP homologues from other species.
- The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes

under stringent conditions to at least about 12 or 25, preferably about 20 or 25, more preferably about 30, 35, 40, 45, 50, 55, 60, 65, or 75 consecutive nucleotides of a sense sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, of an anti-sense sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or of a naturally occurring allelic variant or mutant of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In an exemplary embodiment, a nucleic acid molecule of the present invention comprises a nucleotide sequence which is 350-400,

400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 949, 950-1000, or more nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994.

Probes based on the PCIP nucleotide sequences can be used to detect transcripts or genomic sequences encoding the same or homologous proteins. In preferred embodiments, the probe further comprises a label group attached thereto, *e.g.*, the label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or tissue which misexpress a PCIP protein, such as by measuring a level of a PCIP-encoding nucleic acid in a sample of cells from a subject *e.g.*, detecting PCIP mRNA levels or determining whether a genomic PCIP gene has been mutated or deleted.

A nucleic acid fragment encoding a "biologically active portion of a PCIP protein" can be prepared by isolating a portion of the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, which encodes a polypeptide

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having a PCIP biological activity (the biological activities of the PCIP proteins are described herein), expressing the encoded portion of the PCIP protein (*e.g.*, by recombinant expression *in vitro*) and assessing the activity of the encoded portion of the PCIP protein.

- 5 The invention further encompasses nucleic acid molecules that differ from the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID
- 10 NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, due to degeneracy of the
- 15 genetic code and thus encode the same PCIP proteins as those encoded by the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID
- 20 NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or
- 25 98994. In another embodiment, an isolated nucleic acid molecule of the invention has a nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID
- 30 NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID

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NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72.

- In addition to the PCIP nucleotide sequences shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of the PCIP proteins may exist within a population (*e.g.*, the human population). Such genetic polymorphism in the PCIP genes may exist among individuals within a population due to natural allelic variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules which include an open reading frame encoding a PCIP protein, preferably a mammalian PCIP protein, and can further include non-coding regulatory sequences, and introns.
- Allelic variants of human PCIP include both functional and non-functional PCIP proteins. Functional allelic variants are naturally occurring amino acid sequence variants of the human PCIP protein that maintain the ability to bind a PCIP ligand and/or modulate any of the PCIP activities described herein. Functional allelic variants will typically contain only conservative substitution of one or more amino acids of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or substitution, deletion or insertion of non-critical residues in non-critical regions of the protein.

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Non-functional allelic variants are naturally occurring amino acid sequence variants of the human PCIP protein that do not have the ability to either bind a PCIP ligand and/or modulate any of the PCIP activities described herein. Non-functional allelic variants will typically contain a non-conservative substitution, a deletion, or

5 insertion or premature truncation of the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID

10 NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or a substitution, insertion or deletion in critical residues or critical regions.

The present invention further provides non-human orthologues of the human PCIP protein. Orthologues of the human PCIP protein are proteins that are isolated from non-human organisms and possess the same PCIP ligand binding and/or modulation of

15 potassium channel mediated activities of the human PCIP protein. Orthologues of the human PCIP protein can readily be identified as comprising an amino acid sequence that is substantially identical to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID

20 NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72.

Moreover, nucleic acid molecules encoding other PCIP family members and, thus, which have a nucleotide sequence which differs from the PCIP sequences of SEQ

25 ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID

30 NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936,

98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994 are intended to be within the scope of the invention. For example, another PCIP cDNA can be identified based on the nucleotide sequence of human PCIP. Moreover, nucleic acid molecules encoding PCIP

5 proteins from different species, and thus which have a nucleotide sequence which differs from the PCIP sequences of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID

10 NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or

15 98994 are intended to be within the scope of the invention. For example, a mouse PCIP cDNA can be identified based on the nucleotide sequence of a human PCIP.

Nucleic acid molecules corresponding to natural allelic variants and homologues of the PCIP cDNAs of the invention can be isolated based on their homology to the PCIP nucleic acids disclosed herein using the cDNAs disclosed herein, or a portion

20 thereof, as a hybridization probe according to standard hybridization techniques under stringent hybridization conditions.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 15, 20, 25, 30 or more nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence of

25 SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID

30 NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as

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Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In other embodiment, the nucleic acid is at least 30, 50, 100, 150, 200, 250, 300, 307, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 949, or 950 nucleotides in length. As

5 used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% identical to each other typically remain hybridized to each other. Preferably, the conditions are such that sequences at least about 70%, more preferably at least about 80%, even more preferably at least about 85% or 90% identical to each other typically

10 remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50°C, preferably at 55°C,

15 and more preferably at 60°C or 65°C. Preferably, an isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to the sequence of SEQ ID NO:1 corresponds to a naturally-occurring nucleic acid molecule. As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (*e.g.*, encodes a natural protein).

20 In addition to naturally-occurring allelic variants of the PCIP sequences that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequences of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID

25 NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938,

30 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949,

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98950, 98951, 98991, 98993, or 98994, thereby leading to changes in the amino acid sequence of the encoded PCIP proteins, without altering the functional ability of the PCIP proteins. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in the sequence of SEQ ID NO:1, 5 SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID 10 NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of PCIP (*e.g.*, the 15 sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID 20 NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72) without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are conserved among the PCIP proteins of the present invention, are predicted to be particularly unamenable to alteration. Furthermore, additional amino acid residues that are conserved between the PCIP 25 proteins of the present invention and other members of the PCIP family of proteins are not likely to be amenable to alteration.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding PCIP proteins that contain changes in amino acid residues that are not essential for activity. Such PCIP proteins differ in amino acid sequence from SEQ ID NO:2, SEQ 30 ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID

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NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, yet retain biological activity. In one embodiment, the

5 isolated nucleic acid molecule comprises a nucleotide sequence encoding a protein, wherein the protein comprises an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more identical to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ

10 ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72.

An isolated nucleic acid molecule encoding a PCIP protein homologous to the

15 protein of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID

20 NO:59, SEQ ID NO:70, or SEQ ID NO:72 can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID

25 NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947,

30 98948, 98949, 98950, 98951, 98991, 98993, or 98994, such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein. Mutations

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can be introduced into SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994 by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a PCIP protein is preferably replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of a PCIP coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for PCIP biological activity to identify mutants that retain activity. Following mutagenesis of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID

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NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, the encoded protein can be expressed recombinantly and the

5 activity of the protein can be determined.

In a preferred embodiment, a mutant PCIP protein can be assayed for the ability to (1) interact with (*e.g.*, bind to) a potassium channel protein or portion thereof; (2) regulate the phosphorylation state of a potassium channel protein or portion thereof; (3) associate with (*e.g.*, bind) calcium and, for example, act as a calcium dependent kinase, *e.g.*, phosphorylate a potassium channel in a calcium-dependent manner; (4) associate with (*e.g.*, bind) calcium and, for example, act as a calcium dependent transcription factor; (5) modulate a potassium channel mediated activity in a cell (*e.g.*, a neuronal or cardiac cell) to, for example, beneficially affect the cell; (6) modulate the release of neurotransmitters; (7) modulate membrane excitability; (8) influence the resting potential of membranes; (9) modulate wave forms and frequencies of action potentials; and (10) modulate thresholds of excitation.

In addition to the nucleic acid molecules encoding PCIP proteins described above, another aspect of the invention pertains to isolated nucleic acid molecules which are antisense thereto. An "antisense" nucleic acid comprises a nucleotide sequence which is complementary to a "sense" nucleic acid encoding a protein, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. Accordingly, an antisense nucleic acid can hydrogen bond to a sense nucleic acid. The antisense nucleic acid can be complementary to an entire PCIP coding strand, or to only a portion thereof. In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence encoding PCIP. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence encoding PCIP. The term "noncoding region" refers to 5' and 3' sequences which flank

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the coding region that are not translated into amino acids (*i.e.*, also referred to as 5' and 3' untranslated regions).

Given the coding strand sequences encoding PCIP disclosed herein, antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of PCIP mRNA, but more preferably is an oligonucleotide which is antisense to only a portion of the coding or noncoding region of PCIP mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of PCIP mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5- oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a

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nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a PCIP protein to thereby inhibit expression of the protein, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention include direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

In yet another embodiment, the antisense nucleic acid molecule of the invention is an α -anomeric nucleic acid molecule. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β -units, the strands run parallel to each other (Gaultier *et al.* (1987) *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue *et al.* (1987) *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.* (1987) *FEBS Lett.* 215:327-330).

In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes

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(described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave PCIP mRNA transcripts to thereby inhibit translation of PCIP mRNA. A ribozyme having specificity for a PCIP-encoding nucleic acid can be designed based upon the nucleotide sequence of a PCIP cDNA disclosed herein (*i.e.*,
5 SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID
10 NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the
15 nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a PCIP-encoding mRNA. See, *e.g.*, Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742. Alternatively, PCIP mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, *e.g.*, Bartel, D. and Szostak, J.W. (1993) *Science* 261:1411-1418.
20 Alternatively, PCIP gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the PCIP (*e.g.*, the PCIP promoter and/or enhancers) to form triple helical structures that prevent transcription of the PCIP gene in target cells. See generally, Helene, C. (1991) *Anticancer Drug Des.* 6(6):569-84; Helene, C. *et al.* (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher, L.J. (1992) *Bioassays* 14(12):807-15.

In yet another embodiment, the PCIP nucleic acid molecules of the present invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acid molecules can be modified to
30 generate peptide nucleic acids (see Hyrup B. *et al.* (1996) *Bioorganic & Medicinal Chemistry* 4 (1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs"

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refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *et al.* Proc. Natl. Acad. Sci. 93: 14670-675.

PNAs of PCIP nucleic acid molecules can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, for example, inducing transcription or translation arrest or inhibiting replication. PNAs of PCIP nucleic acid molecules can also be used in the analysis of single base pair mutations in a gene, (*e.g.*, by PNA-directed PCR clamping); as 'artificial restriction enzymes' when used in combination with other enzymes, (*e.g.*, S1 nucleases (Hyrup B. (1996) *supra*)); or as probes or primers for DNA sequencing or hybridization (Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *supra*).

In another embodiment, PNAs of PCIP can be modified, (*e.g.*, to enhance their stability or cellular uptake), by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras of PCIP nucleic acid molecules can be generated which may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, (*e.g.*, RNase H and DNA polymerases), to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup B. (1996) *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup B. (1996) *supra* and Finn P.J. *et al.* (1996) *Nucleic Acids Res.* 24 (17): 3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs, *e.g.*, 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite, can be used as a between the PNA and the 5' end of DNA (Mag, M. *et*

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al. (1989) *Nucleic Acid Res.* 17: 5973-88). PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn P.J. *et al.* (1996) *supra*). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser, K.H. *et al.* (1975)

5 *Bioorganic Med. Chem. Lett.* 5: 1119-11124).

In other embodiments, the oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.* (1989) *Proc. Natl. Acad. Sci. US.* 86:6553-6556; Lemaitre *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:648-652;

10 PCT Publication No. W088/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. W089/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (See, *e.g.*, Krol *et al.* (1988) *Bio-Techniques* 6:958-976) or intercalating agents. (See, *e.g.*, Zon (1988) *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, (*e.g.*, a peptide, hybridization
15 triggered cross-linking agent, transport agent, or hybridization-triggered cleavage agent).

II. Isolated PCIP Proteins and Anti-PCIP Antibodies

One aspect of the invention pertains to isolated PCIP proteins, and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens
20 to raise anti-PCIP antibodies. In one embodiment, native PCIP proteins can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, PCIP proteins are produced by recombinant DNA techniques. Alternative to recombinant expression, a PCIP protein or polypeptide can be synthesized chemically using standard peptide synthesis techniques.

25 An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the PCIP protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. The language
"substantially free of cellular material" includes preparations of PCIP protein in which
30 the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. In one embodiment, the language "substantially free of

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cellular material" includes preparations of PCIP protein having less than about 30% (by dry weight) of non-PCIP protein (also referred to herein as a "contaminating protein"), more preferably less than about 20% of non-PCIP protein, still more preferably less than about 10% of non-PCIP protein, and most preferably less than about 5% non-PCIP

- 5 protein. When the PCIP protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, more preferably less than about 10%, and most preferably less than about 5% of the volume of the protein preparation.

- The language "substantially free of chemical precursors or other chemicals"10 includes preparations of PCIP protein in which the protein is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of PCIP protein having less than about 30% (by dry weight) of chemical precursors or non-PCIP chemicals, more preferably less than about 20%15 chemical precursors or non-PCIP chemicals, still more preferably less than about 10% chemical precursors or non-PCIP chemicals, and most preferably less than about 5% chemical precursors or non-PCIP chemicals.

- As used herein, a "biologically active portion" of a PCIP protein includes a fragment of a PCIP protein which participates in an interaction between a PCIP20 molecule and a non-PCIP molecule. Biologically active portions of a PCIP protein include peptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the PCIP protein, *e.g.*, the amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID25 NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, which include less amino acids than the full length PCIP proteins, and exhibit at least one activity of a PCIP protein. Typically,30 biologically active portions comprise a domain or motif with at least one activity of the PCIP protein, *e.g.*, binding of a potassium channel subunit. A biologically active

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portion of a PCIP protein can be a polypeptide which is, for example, 10, 25, 50, 100, 200, or more amino acids in length. Biologically active portions of a PCIP protein can be used as targets for developing agents which modulate a potassium channel mediated activity.

- 5 In one embodiment, a biologically active portion of a PCIP protein comprises at least one calcium binding domain.

 It is to be understood that a preferred biologically active portion of a PCIP protein of the present invention may contain at least one of the above-identified structural domains. A more preferred biologically active portion of a PCIP protein may
10 contain at least two of the above-identified structural domains. Moreover, other biologically active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of a native PCIP protein.

- In a preferred embodiment, the PCIP protein has an amino acid sequence shown
15 in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID
20 NO:59, SEQ ID NO:70, or SEQ ID NO:72. In other embodiments, the PCIP protein is substantially homologous to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID
25 NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, and retains the functional activity of the protein of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID
30 NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID

NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, yet differs in amino acid sequence due to natural allelic variation or mutagenesis, as described in detail in subsection I above. Accordingly, in another embodiment, the PCIP protein is a protein which comprises an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more identical to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72.

Isolated proteins of the present invention, preferably 1v, 9q, p19, W28559, KChIP4a, KChIP4b, 33b07, 1p, or 7s proteins, have an amino acid sequence sufficiently identical to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or are encoded by a nucleotide sequence sufficiently identical to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71. As used herein, the term "sufficiently identical" refers to a first amino acid or nucleotide sequence which contains a sufficient or minimum number of identical or equivalent (*e.g.*, an amino acid residue which has a similar side chain) amino acid residues or nucleotides to a second amino acid or nucleotide sequence such that the first and second amino acid or nucleotide sequences share common structural domains or motifs and/or a common functional activity. For example, amino acid or nucleotide sequences which share common structural domains

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have at least 30%, 40%, or 50% identity, preferably 60% identity, more preferably 70%-80%, and even more preferably 90-95% identity across the amino acid sequences of the domains and contain at least one and preferably two structural domains or motifs, are defined herein as sufficiently identical. Furthermore, amino acid or nucleotide sequences
 5 which share at least 30%, 40%, or 50%, preferably 60%, more preferably 70-80%, or 90-95% identity and share a common functional activity are defined herein as sufficiently identical.

Preferred proteins are PCIP proteins having at least one calcium binding domain and, preferably, a PCIP activity. Other preferred proteins are PCIP proteins having at least
 10 one calcium binding domain, and are, preferably, encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID
 15 NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71.

To determine the percent identity of two amino acid sequences or of two nucleic
 20 acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more
 25 preferably at least 50%, even more preferably at least 60%, and even more preferably at least 70%, 80%, or 90% of the length of the reference sequence (e.g., when aligning a second sequence to the PCIP amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID
 30 NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID

NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 having 177 amino acid residues, at least 80, preferably at least 100, more preferably at least 120, even more preferably at least 140, and even more preferably at least 150, 160 or 170 amino acid residues are aligned). The amino acid residues or
5 nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology"). The percent identity
10 between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred
15 embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at <http://www.gcg.com>), using either a Blosum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet
20 another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (available at <http://www.gcg.com>), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the
25 algorithm of E. Meyers and W. Miller (CABIOS, 4:11-17 (1989)) which has been incorporated into the ALIGN program (version 2.0 or 2.0U), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example,
30 identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J.*

Mol. Biol. 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to PCIP nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain

5 amino acid sequences homologous to PCIP protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. See <http://www.ncbi.nlm.nih.gov>.

10 The invention also provides PCIP chimeric or fusion proteins. As used herein, a PCIP "chimeric protein" or "fusion protein" comprises a PCIP polypeptide operatively linked to a non-PCIP polypeptide. An "PCIP polypeptide" refers to a polypeptide having an amino acid sequence corresponding to PCIP, whereas a "non-PCIP polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a

15 protein which is not substantially homologous to the PCIP protein, *e.g.*, a protein which is different from the PCIP protein and which is derived from the same or a different organism. Within a PCIP fusion protein the PCIP polypeptide can correspond to all or a portion of a PCIP protein. In a preferred embodiment, a PCIP fusion protein comprises at least one biologically active portion of a PCIP protein. In another preferred

20 embodiment, a PCIP fusion protein comprises at least two biologically active portions of a PCIP protein. Within the fusion protein, the term "operatively linked" is intended to indicate that the PCIP polypeptide and the non-PCIP polypeptide are fused in-frame to each other. The non-PCIP polypeptide can be fused to the N-terminus or C-terminus of the PCIP polypeptide.

25 For example, in one embodiment, the fusion protein is a GST-PCIP fusion protein in which the PCIP sequences are fused to the C-terminus of the GST sequences. Such fusion proteins can facilitate the purification of recombinant PCIP.

In another embodiment, the fusion protein is a PCIP protein containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian

30 host cells), expression and/or secretion of PCIP can be increased through use of a heterologous signal sequence.

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The PCIP fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject *in vivo*. The PCIP fusion proteins can be used to affect the bioavailability of a PCIP substrate. Use of PCIP fusion proteins may be useful therapeutically for the treatment of potassium channel associated disorders such as CNS disorders, *e.g.*, neurodegenerative disorders such as Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, spinocerebellar ataxia, and Jakob-Creutzfeldt disease; psychiatric disorders, *e.g.*, depression, schizophrenic disorders, Korsakoff's psychosis, mania, anxiety disorders, or phobic disorders; learning or memory disorders, *e.g.*, amnesia or age-related memory loss; and neurological disorders; *e.g.*, migraine. Use of PCIP fusion proteins may also be useful therapeutically for the treatment of potassium channel associated disorders such as cardiovascular disorders, *e.g.*, arteriosclerosis, ischemia reperfusion injury, restenosis, arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, atrial fibrillation or congestive heart failure.

Moreover, the PCIP-fusion proteins of the invention can be used as immunogens to produce anti-PCIP antibodies in a subject, to purify PCIP ligands and in screening assays to identify molecules which inhibit the interaction of PCIP with a PCIP substrate.

Preferably, a PCIP chimeric or fusion protein of the invention is produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, for example by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene

fragments which can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel *et al.* John Wiley & Sons: 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST polypeptide). A PCIP-
5 encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the PCIP protein.

The present invention also pertains to variants of the PCIP proteins which function as either PCIP agonists (mimetics) or as PCIP antagonists. Variants of the PCIP proteins can be generated by mutagenesis, e.g., discrete point mutation or
10 truncation of a PCIP protein. An agonist of the PCIP proteins can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of a PCIP protein. An antagonist of a PCIP protein can inhibit one or more of the activities of the naturally occurring form of the PCIP protein by, for example, competitively modulating a potassium channel mediated activity of a PCIP protein. Thus, specific
15 biological effects can be elicited by treatment with a variant of limited function. In one embodiment, treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein has fewer side effects in a subject relative to treatment with the naturally occurring form of the PCIP protein.

In one embodiment, variants of a PCIP protein which function as either PCIP
20 agonists (mimetics) or as PCIP antagonists can be identified by screening combinatorial libraries of mutants, e.g., truncation mutants, of a PCIP protein for PCIP protein agonist or antagonist activity. In one embodiment, a variegated library of PCIP variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of PCIP variants can be produced by, for
25 example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential PCIP sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (e.g., for phage display) containing the set of PCIP sequences therein. There are a variety of methods which can be used to produce libraries of potential PCIP variants from a degenerate
30 oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an

appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential PCIP sequences. Methods for synthesizing degenerate oligonucleotides are known in the art (see, e.g., Narang, S.A. (1983) *Tetrahedron* 39:3; Itakura *et al.* (1984) *Annu. Rev.*

- 5 *Biochem.* 53:323; Itakura *et al.* (1984) *Science* 198:1056; Ike *et al.* (1983) *Nucleic Acid Res.* 11:477.

- In addition, libraries of fragments of a PCIP protein coding sequence can be used to generate a variegated population of PCIP fragments for screening and subsequent selection of variants of a PCIP protein. In one embodiment, a library of coding sequence
10 fragments can be generated by treating a double stranded PCR fragment of a PCIP coding sequence with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with
15 S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes N-terminal, C-terminal and internal fragments of various sizes of the PCIP protein.

- Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA
20 libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of PCIP proteins. The most widely used techniques, which are amenable to high throughput analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting
25 library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a new technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify PCIP variants (Arkin and Yourvan
30 (1992) *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.* (1993) *Protein Engineering* 6(3):327-331).

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In one embodiment, cell based assays can be exploited to analyze a variegated PCIP library. For example, a library of expression vectors can be transfected into a cell line which ordinarily possesses a potassium channel mediated activity. The effect of the PCIP mutant on the potassium channel mediated activity can then be detected, *e.g.*, by any of a number of enzymatic assays or by detecting the release of a neurotransmitter. Plasmid DNA can then be recovered from the cells which score for inhibition, or alternatively, potentiation of the potassium channel mediated activity, and the individual clones further characterized.

- An isolated PCIP protein, or a portion or fragment thereof, can be used as an immunogen to generate antibodies that bind PCIP using standard techniques for polyclonal and monoclonal antibody preparation. A full-length PCIP protein can be used or, alternatively, the invention provides antigenic peptide fragments of PCIP for use as immunogens. The antigenic peptide of PCIP comprises at least 8 amino acid residues of the amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 and encompasses an epitope of PCIP such that an antibody raised against the peptide forms a specific immune complex with PCIP. Preferably, the antigenic peptide comprises at least 10 amino acid residues, more preferably at least 15 amino acid residues, even more preferably at least 20 amino acid residues, and most preferably at least 30 amino acid residues.
- Preferred epitopes encompassed by the antigenic peptide are regions of PCIP that are located on the surface of the protein, *e.g.*, hydrophilic regions, as well as regions with high antigenicity.

- A PCIP immunogen typically is used to prepare antibodies by immunizing a suitable subject, (*e.g.*, rabbit, goat, mouse or other mammal) with the immunogen. An appropriate immunogenic preparation can contain, for example, recombinantly expressed PCIP protein or a chemically synthesized PCIP polypeptide. The preparation

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can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar immunostimulatory agent. Immunization of a suitable subject with an immunogenic PCIP preparation induces a polyclonal anti-PCIP antibody response.

Accordingly, another aspect of the invention pertains to anti-PCIP antibodies.

- 5 The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site which specifically binds (immunoreacts with) an antigen, such as PCIP. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')₂ fragments which can be generated by treating the
- 10 antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies that bind PCIP. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of PCIP. A monoclonal antibody composition
- 15 thus typically displays a single binding affinity for a particular PCIP protein with which it immunoreacts.

- Polyclonal anti-PCIP antibodies can be prepared as described above by immunizing a suitable subject with a PCIP immunogen. The anti-PCIP antibody titer in the immunized subject can be monitored over time by standard techniques, such as with
- 20 an enzyme linked immunosorbent assay (ELISA) using immobilized PCIP. If desired, the antibody molecules directed against PCIP can be isolated from the mammal (*e.g.*, from the blood) and further purified by well known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, *e.g.*, when the anti-PCIP antibody titers are highest, antibody-producing cells can be
 - 25 obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497) (see also, Brown *et al.* (1981) *J. Immunol.* 127:539-46; Brown *et al.* (1980) *J. Biol. Chem.* 255:4980-83; Yeh *et al.* (1976) *Proc. Natl. Acad. Sci. USA* 76:2927-31; and Yeh *et al.* (1982) *Int. J. Cancer* 29:269-75), the
 - 30 more recent human B cell hybridoma technique (Kozbor *et al.* (1983) *Immunol Today* 4:72), the EBV-hybridoma technique (Cole *et al.* (1985), *Monoclonal Antibodies and*

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Cancer Therapy, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing monoclonal antibody hybridomas is well known (see generally R. H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); E. A. Lerner (1981) *Yale J. Biol. Med.*, 54:387-402; M. L. Gefter *et al.* (1977) *Somatic Cell Genet.* 3:231-36). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with a PCIP immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds PCIP.

- 10 Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating an anti-PCIP monoclonal antibody (see, *e.g.*, G. Galfre *et al.* (1977) *Nature* 266:55052; Gefter *et al.* *Somatic Cell Genet.*, cited *supra*; Lerner, *Yale J. Biol. Med.*, cited *supra*; Kenneth, *Monoclonal Antibodies*, cited *supra*). Moreover, the ordinarily skilled worker will
- 15 appreciate that there are many variations of such methods which also would be useful. Typically, the immortal cell line (*e.g.*, a myeloma cell line) is derived from the same mammalian species as the lymphocytes. For example, murine hybridomas can be made by fusing lymphocytes from a mouse immunized with an immunogenic preparation of the present invention with an immortalized mouse cell line. Preferred immortal cell
- 20 lines are mouse myeloma cell lines that are sensitive to culture medium containing hypoxanthine, aminopterin and thymidine ("HAT medium"). Any of a number of myeloma cell lines can be used as a fusion partner according to standard techniques, *e.g.*, the P3-NS1/1-Ag4-1, P3-x63-Ag8.653 or Sp2/O-Ag14 myeloma lines. These myeloma lines are available from ATCC. Typically, HAT-sensitive mouse myeloma
- 25 cells are fused to mouse splenocytes using polyethylene glycol ("PEG"). Hybridoma cells resulting from the fusion are then selected using HAT medium, which kills unfused and unproductively fused myeloma cells (unfused splenocytes die after several days because they are not transformed). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for
- 30 antibodies that bind PCIP, *e.g.*, using a standard ELISA assay.

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- Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal anti-PCIP antibody can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with PCIP to thereby isolate immunoglobulin library members that bind PCIP.
- 5 Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™ Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, Ladner *et al.* U.S.
 - 10 Patent No. 5,223,409; Kang *et al.* PCT International Publication No. WO 92/18619; Dower *et al.* PCT International Publication No. WO 91/17271; Winter *et al.* PCT International Publication WO 92/20791; Markland *et al.* PCT International Publication No. WO 92/15679; Breitling *et al.* PCT International Publication WO 93/01288; McCafferty *et al.* PCT International Publication No. WO 92/01047; Garrard *et al.* PCT
 - 15 International Publication No. WO 92/09690; Ladner *et al.* PCT International Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; Griffiths *et al.* (1993) *EMBO J* 12:725-734; Hawkins *et al.* (1992) *J. Mol. Biol.* 226:889-896; Clarkson *et al.* (1991) *Nature* 352:624-628; Gram *et al.* (1992) *Proc. Natl. Acad.*
 - 20 *Sci. USA* 89:3576-3580; Garrard *et al.* (1991) *Bio/Technology* 9:1373-1377; Hoogenboom *et al.* (1991) *Nuc. Acid Res.* 19:4133-4137; Barbas *et al.* (1991) *Proc. Natl. Acad. Sci. USA* 88:7978-7982; and McCafferty *et al.* *Nature* (1990) 348:552-554.
- Additionally, recombinant anti-PCIP antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be
- 25 made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in Robinson *et al.* International Application No. PCT/US86/02269; Akira, *et al.* European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496;
 - 30 Morrison *et al.* European Patent Application 173,494; Neuberger *et al.* PCT International Publication No. WO 86/01533; Cabilly *et al.* U.S. Patent No. 4,816,567;

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Cabilly *et al.* European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.* (1987) *J. Immunol.* 139:3521-3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Canc. Res.* 47:999-1005; Wood *et al.* (1985) *Nature* 314:446-449; and Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559; Morrison, S. L. (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *BioTechniques* 4:214; Winter U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeven *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

- An anti-PCIP antibody (*e.g.*, monoclonal antibody) can be used to isolate PCIP by standard techniques, such as affinity chromatography or immunoprecipitation. An anti-PCIP antibody can facilitate the purification of natural PCIP from cells and of recombinantly produced PCIP expressed in host cells. Moreover, an anti-PCIP antibody can be used to detect PCIP protein (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the PCIP protein. Anti-PCIP antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

III. Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a PCIP protein (or a portion thereof). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting
5 another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial
10 vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "expression
15 vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-
20 associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory
sequences, selected on the basis of the host cells to be used for expression, which is
25 operatively linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory
30 sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for

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example, in Goeddel; *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and those which direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (e.g., PCIP proteins, mutant forms of PCIP proteins, fusion proteins, and the like).

The recombinant expression vectors of the invention can be designed for expression of PCIP proteins in prokaryotic or eukaryotic cells. For example, PCIP proteins can be expressed in bacterial cells such as *E. coli*, insect cells (using baculovirus expression vectors) yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith, D.B.

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and Johnson, K.S. (1988) *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

- Purified fusion proteins can be utilized in PCIP activity assays, (e.g., direct assays or competitive assays described in detail below), or to generate antibodies specific for PCIP proteins, for example. In a preferred embodiment, a PCIP fusion protein expressed in a retroviral expression vector of the present invention can be utilized to infect bone marrow cells which are subsequently transplanted into irradiated recipients. The pathology of the subject recipient is then examined after sufficient time has passed (e.g., six (6) weeks).

- Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann *et al.*, (1988) *Gene* 69:301-315) and pET 11d (Studier *et al.*, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 60-89). Target gene expression from the pTrc vector relies on host RNA polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a coexpressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident prophage harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

- One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, S., *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 119-128). Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada *et al.*, (1992) *Nucleic Acids Res.* 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

- In another embodiment, the PCIP expression vector is a yeast expression vector. Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1 (Baldari, *et*

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al., (1987) *Embo J.* 6:229-234), pMFa (Kurjan and Herskowitz, (1982) *Cell* 30:933-943), pJRY88 (Schultz *et al.*, (1987) *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, CA), and picZ (InVitrogen Corp, San Diego, CA).

Alternatively, PCIP proteins can be expressed in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (*e.g.*, Sf9 cells) include the pAc series (Smith *et al.* (1983) *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers (1989) *Virology* 170:31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, B. (1987) *Nature* 329:840) and pMT2PC (Kaufman *et al.* (1987) *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert *et al.* (1987) *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame and Eaton (1988) *Adv. Immunol.* 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore (1989) *EMBO J.* 8:729-733) and immunoglobulins (Banerji *et al.* (1983) *Cell* 33:729-740; Queen and Baltimore (1983) *Cell* 33:741-748), neuron-specific promoters (*e.g.*, the neurofilament promoter; Byrne and Ruddle (1989) *Proc. Natl. Acad. Sci. USA* 86:5473-5477), pancreas-specific promoters (Edlund *et al.* (1985) *Science* 230:912-916), and mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-

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regulated promoters are also encompassed, for example the murine hox promoters (Kessel and Gruss (1990) *Science* 249:374-379) and the α -fetoprotein promoter (Campes and Tilghman (1989) *Genes Dev.* 3:537-546).

The invention further provides a recombinant expression vector comprising a

5 DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to PCIP mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub, H. *et al.*, Antisense RNA as a molecular tool for genetic analysis, *Reviews - Trends in Genetics*, Vol. 1(1) 1986.

Another aspect of the invention pertains to host cells into which a recombinant
20 expression vector of the invention has been introduced. The terms "host cell" and
"recombinant host cell" are used interchangeably herein. It is understood that such
terms refer not only to the particular subject cell but to the progeny or potential progeny
of such a cell. Because certain modifications may occur in succeeding generations due
to either mutation or environmental influences, such progeny may not, in fact, be
25 identical to the parent cell, but are still included within the scope of the term as used
herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, a PCIP protein can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*Molecular Cloning: A Laboratory Manual*, 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989), and other laboratory manuals.

- For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be introduced into a host cell on the same vector as that encoding a PCIP protein or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

- A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) a PCIP protein. Accordingly, the invention further provides methods for producing a PCIP protein using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding a PCIP protein has been introduced) in a suitable medium such that a PCIP protein is produced. In another embodiment, the method further comprises isolating a PCIP protein from the medium or the host cell.

- The host cells of the invention can also be used to produce non-human transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which PCIP-coding sequences have been

introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous PCIP sequences have been introduced into their genome or homologous recombinant animals in which endogenous PCIP sequences have been altered. Such animals are useful for studying the function and/or activity of a PCIP and for identifying and/or evaluating modulators of PCIP activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, and the like. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous PCIP gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing a PCIP-encoding nucleic acid into the male pronuclei of a fertilized oocyte, e.g., by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. The PCIP cDNA sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 can be introduced as a transgene into the genome of a non-human animal. Alternatively, a nonhuman homologue of a human PCIP gene, such as a mouse or rat PCIP gene, can be used as a transgene. Alternatively, a PCIP gene homologue, such as another PCIP family member, can be isolated based on hybridization to the PCIP cDNA sequences of SEQ ID NO:1, SEQ ID NO:3 SEQ ID

NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994 (described further in subsection I above) and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to a PCIP transgene to direct expression of a PCIP protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Patent No. 4,873,191 by Wagner *et al.* and in Hogan, B., *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of a PCIP transgene in its genome and/or expression of PCIP mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding a PCIP protein can further be bred to other transgenic animals carrying other transgenes.

To create a homologous recombinant animal, a vector is prepared which contains at least a portion of a PCIP gene into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the PCIP gene. The PCIP gene can be a human gene (*e.g.*, the cDNA of SEQ ID NO:1), but more preferably, is a non-human homologue of a human PCIP gene (*e.g.*, the cDNA of SEQ ID NO:3 or 5). For example, a mouse PCIP gene can be used to construct a homologous recombination vector suitable for altering an endogenous PCIP gene in the mouse genome. In a preferred embodiment, the vector is designed such that, upon homologous

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recombination, the endogenous PCIP gene is functionally disrupted (*i.e.*, no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous PCIP gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous PCIP protein). In the homologous recombination vector, the altered portion of the PCIP gene is flanked at its 5' and 3' ends by additional nucleic acid sequence of the PCIP gene to allow for homologous recombination to occur between the exogenous PCIP gene carried by the vector and an endogenous PCIP gene in an embryonic stem cell. The additional flanking PCIP nucleic acid sequence is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see *e.g.*, Thomas, K.R. and Capecchi, M. R. (1987) *Cell* 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced PCIP gene has homologously recombined with the endogenous PCIP gene are selected (see *e.g.*, Li, E. *et al.* (1992) *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras (see *e.g.*, Bradley, A. in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E.J. Robertson, ed. (IRL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, A. (1991) *Current Opinion in Biotechnology* 2:823-829 and in PCT International Publication Nos.: WO 90/11354 by Le Mouellec *et al.*; WO 91/01140 by Smithies *et al.*; WO 92/0968 by Zijlstra *et al.*; and WO 93/04169 by Berns *et al.*

In another embodiment, transgenic non-humans animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For

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a description of the *cre/loxP* recombinase system, see, *e.g.*, Lakso *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.* (1991) *Science* 251:1351-1355. If a *cre/loxP* recombinase system is used to regulate expression of the

5 transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, *e.g.*, by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

10 Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, I. *et al.* (1997) *Nature* 385:810-813 and PCT International Publication Nos. WO 97/07668 and WO 97/07669. In brief, a cell, *e.g.*, a somatic cell, from the transgenic animal can be isolated and induced to exit the growth cycle and enter G₀ phase. The quiescent cell can then be fused, *e.g.*, through

15 the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyte and then transferred to pseudopregnant female foster animal. The offspring borne of this female foster animal will be a clone of the animal from which the cell, *e.g.*, the somatic cell, is isolated.

20

IV. Pharmaceutical Compositions

The PCIP nucleic acid molecules, fragments of PCIP proteins, and anti-PCIP antibodies (also referred to herein as "active compounds") of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such

25 compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and

30 agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof

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in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include

- 5 parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents;
- 10 antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be
- 15 enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For

- 20 intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as
- 25 bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of
- 30 surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol,

ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for

- 5 example, aluminum monostearate and gelatin.

 Sterile injectable solutions can be prepared by incorporating the active compound (*e.g.*, a fragment of a PCIP protein or an anti-PCIP antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared
10 by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously
15 sterile-filtered solution thereof.

 Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared
20 using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as
25 microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

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For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For
5 transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active
10 compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

15 In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid.
20 Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled
25 in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound
30 calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are

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dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

Toxicity and therapeutic efficacy of such compounds can be determined by
5 standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit large therapeutic indices are preferred. While
10 compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies
15 preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a
20 circulating plasma concentration range that includes the IC50 (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

25 As defined herein, a therapeutically effective amount of protein or polypeptide (*i.e.*, an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight, and even more preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight. The skilled artisan will appreciate that certain
30 factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health

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and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a protein, polypeptide, or antibody can include a single treatment or, preferably, can include a series of treatments.

In a preferred example, a subject is treated with antibody, protein, or polypeptide in the range of between about 0.1 to 20 mg/kg body weight, one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated that the effective dosage of antibody, protein, or polypeptide used for treatment may increase or decrease over the course of a particular treatment. Changes in dosage may result and become apparent from the results of diagnostic assays as described herein.

The present invention encompasses agents which modulate expression or activity. An agent may, for example, be a small molecule. For example, such small molecules include, but are not limited to, peptides, peptidomimetics, amino acids, amino acid analogs, polynucleotides, polynucleotide analogs, nucleotides, nucleotide analogs, organic or inorganic compounds (i.e., including heteroorganic and organometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds.

It is understood that appropriate doses of small molecule agents depends upon a number of factors within the ken of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of the small molecule will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner desires the small molecule to have upon the nucleic acid or polypeptide of the invention.

Exemplary doses include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (*e.g.*, about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram.

5 It is

furthermore understood that appropriate doses of a small molecule depend upon the potency of the small molecule with respect to the expression or activity to be modulated. Such appropriate doses may be determined using the assays described herein. When one or more of these small molecules is to be administered to an animal (*e.g.*, a human) in

10 order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of
15 the specific compound employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

Further, an antibody (or fragment thereof) may be conjugated to a therapeutic
20 moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone,
25 glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan,
30 dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and

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doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthracycline (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62:119-58 (1982). Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980.

The nucleic acid molecules of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (see U.S. Patent 5,328,470) or by

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stereotactic injection (see *e.g.*, Chen *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery

5 vector can be produced intact from recombinant cells, *e.g.*, retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

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V. Uses and Methods of the Invention

The nucleic acid molecules, proteins, protein homologues, and antibodies described herein can be used in one or more of the following methods: a) screening assays; b) predictive medicine (*e.g.*, diagnostic assays, prognostic assays, monitoring

15 clinical trials, and pharmacogenetics); and c) methods of treatment (*e.g.*, therapeutic and prophylactic). As described herein, a PCIP protein of the invention has one or more of the following activities: (1) it interacts with (*e.g.*, binds to) a potassium channel protein or portion thereof; (2) it regulates the phosphorylation state of a potassium channel protein or portion thereof; (3) it associates with (*e.g.*, binds to) calcium and can, for

20 example, act as a calcium dependent kinase, *e.g.*, phosphorylate a potassium channel or a G-protein coupled receptor in a calcium-dependent manner; (4) it associates with (*e.g.*, binds to) calcium and can, for example, act as a calcium dependent transcription factor; (5) it modulates a potassium channel mediated activity in a cell (*e.g.*, a neuronal or cardiac cell) to, for example, beneficially affect the cell; (6) it modulates chromatin

25 formation in a cell, *e.g.*, a neuronal or cardiac cell; (7) it modulates vesicular traffic and protein transport in a cell, *e.g.*, a neuronal or cardiac cell; (8) it modulates cytokine signaling in a cell, *e.g.*, a neuronal or cardiac cell; (9) it regulates the association of a potassium channel protein or portion thereof with the cellular cytoskeleton; (10) it modulates cellular proliferation; (11) it modulates the release of neurotransmitters; (12)

30 it modulates membrane excitability; (13) it influences the resting potential of membranes; (14) it modulates wave forms and frequencies of action potentials; and (15)

- it modulates thresholds of excitation and, thus, can be used to, for example, (1) modulate the activity of a potassium channel protein or portion thereof; (2) modulate the phosphorylation state of a potassium channel protein or portion thereof; (3) modulate the phosphorylation state of a potassium channel or a G-protein coupled receptor in a
- 5 calcium-dependent manner; (4) associate with (*e.g.*, bind to) calcium and act as a calcium dependent transcription factor; (5) modulate a potassium channel mediated activity in a cell (*e.g.*, a neuronal or cardiac cell) to, for example, beneficially affect the cell; (6) modulate chromatin formation in a cell, *e.g.*, a neuronal or cardiac cell; (7) modulate vesicular traffic and protein transport in a cell, *e.g.*, a neuronal or cardiac cell;
 - 10 (8) modulate cytokine signaling in a cell, *e.g.*, a neuronal or cardiac cell; (9) regulate the association of a potassium channel protein or portion thereof with the cellular cytoskeleton; (10) modulate cellular proliferation; (11) modulate the release of neurotransmitters; (12) modulate membrane excitability; (13) influence the resting potential of membranes; (14) modulate wave forms and frequencies of action potentials;
 - 15 and (15) modulate thresholds of excitation.

- The isolated nucleic acid molecules of the invention can be used, for example, to express PCIP protein (*e.g.*, via a recombinant expression vector in a host cell in gene therapy applications), to detect PCIP mRNA (*e.g.*, in a biological sample) or a genetic alteration in a PCIP gene, and to modulate PCIP activity, as described further below.
- 20 The PCIP proteins can be used to treat disorders characterized by insufficient or excessive production of a PCIP substrate or production of PCIP inhibitors. In addition, the PCIP proteins can be used to screen for naturally occurring PCIP substrates, to screen for drugs or compounds which modulate PCIP activity, as well as to treat disorders characterized by insufficient or excessive production of PCIP protein or
 - 25 production of PCIP protein forms which have decreased or aberrant activity compared to PCIP wild type protein (*e.g.*, CNS disorders such as neurodegenerative disorders, *e.g.*, Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, spinocerebellar ataxia, and
 - 30 Jakob-Creutzfeldt disease; psychiatric disorders, *e.g.*, depression, schizophrenic disorders, Korsakoff's psychosis, mania, anxiety disorders, bipolar affective disorders, or

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phobic disorders; learning or memory disorders, *e.g.*, amnesia or age-related memory loss; neurological disorders, *e.g.*, migraine; pain disorders, *e.g.*, hyperalgesia or pain associated with musculoskeletal disorders; spinal cord injury; stroke; and head trauma; or cardiovascular disorders such as sinus node disfunction, angina, heart failure,

- 5 hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrhythmia). Moreover, the anti-PCIP antibodies of the invention can be used to detect and isolate PCIP proteins, regulate the bioavailability of PCIP proteins, and modulate PCIP activity.

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A. Screening Assays:

- The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, small molecules or other drugs) which bind to PCIP proteins, have a
15 stimulatory or inhibitory effect on, for example, PCIP expression or PCIP activity, or have a stimulatory or inhibitory effect on, for example, the expression or activity of PCIP substrate.

- In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a PCIP protein or polypeptide or biologically active
20 portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of a PCIP protein or polypeptide or biologically active portion thereof. The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable
25 parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S. (1997)
30 *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (*e.g.*, Houghten (1992) *Biotechniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (Ladner USP 5,223,409), spores (Ladner USP '409), plasmids (Cull *et al.* (1992) *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith (1990) *Science* 249:386-390); (Devlin (1990) *Science* 249:404-406); (Cwirla *et al.* (1990) *Proc. Natl. Acad. Sci.* 87:6378-6382); (Felici (1991) *J. Mol. Biol.* 222:301-310); (Ladner *supra.*).

In one embodiment, an assay is a cell-based assay in which a cell which expresses a PCIP protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate PCIP activity, *e.g.*, binding to a potassium channel or a portion thereof, is determined. Determining the ability of the test compound to modulate PCIP activity can be accomplished by monitoring, for example, the release of a neurotransmitter, *e.g.*, dopamine, from a cell which expresses PCIP such as a neuronal cell, *e.g.*, a substantia nigra neuronal cell, or a cardiac cell. Furthermore, determining the ability of the test compound to modulate PCIP activity can be accomplished by monitoring, for example, the I_{to} current or the release of a neurotransmitter from a cell which expresses PCIP such as a cardiac cell. Currents in cells, *e.g.*, the I_{to} current, can be measured using the patch-clamp technique as described in the Examples section using the techniques described in, for example, Hamill *et al.* 1981. *Pfluegers Arch.* 391: 85-100). The cell, for example, can be of mammalian origin. Determining the ability of the test compound to modulate the ability of PCIP to bind to a substrate can be accomplished, for example, by coupling the PCIP substrate with a radioisotope or enzymatic label such that binding of the PCIP substrate to PCIP can be determined by detecting the labeled PCIP substrate in a complex. For example, compounds (*e.g.*, PCIP substrates) can be labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either

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directly or indirectly, and the radioisotope detected by direct counting of radioemmission or by scintillation counting. Alternatively, compounds can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

It is also within the scope of this invention to determine the ability of a compound (*e.g.*, PCIP substrate) to interact with PCIP without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a compound with PCIP without the labeling of either the compound or the PCIP.

- 10 McConnell, H. M. *et al.* (1992) *Science* 257:1906-1912. As used herein, a "microphysiometer" (*e.g.*, Cytosensor) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between a compound and PCIP.

- 15 In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a PCIP target molecule (*e.g.*, a potassium channel or a fragment thereof) with a test compound and determining the ability of the test compound to modulate (*e.g.* stimulate or inhibit) the activity of the PCIP target molecule. Determining the ability of the test compound to modulate the activity of a PCIP target molecule can be
- 20 accomplished, for example, by determining the ability of the PCIP protein to bind to or interact with the PCIP target molecule, *e.g.*, a potassium channel or a fragment thereof.

- Determining the ability of the PCIP protein or a biologically active fragment thereof, to bind to or interact with a PCIP target molecule can be accomplished by one of the methods described above for determining direct binding. In a preferred embodiment,
- 25 determining the ability of the PCIP protein to bind to or interact with a PCIP target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (*i.e.*, intracellular Ca^{2+} , diacylglycerol, IP_3 , and the like), detecting catalytic/enzymatic activity of the target an appropriate substrate,
- 30 detecting the induction of a reporter gene (comprising a target-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, *e.g.*,

luciferase), or detecting a target-regulated cellular response such as the release of a neurotransmitter.

In yet another embodiment, an assay of the present invention is a cell-free assay in which a PCIP protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to bind to the PCIP protein or biologically active portion thereof is determined. Preferred biologically active portions of the PCIP proteins to be used in assays of the present invention include fragments which participate in interactions with non-PCIP molecules, *e.g.*, potassium channels or fragments thereof, or fragments with high surface probability scores. Binding of the test compound to the PCIP protein can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting the PCIP protein or biologically active portion thereof with a known compound which binds PCIP to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a PCIP protein, wherein determining the ability of the test compound to interact with a PCIP protein comprises determining the ability of the test compound to preferentially bind to PCIP or biologically active portion thereof as compared to the known compound.

In another embodiment, the assay is a cell-free assay in which a PCIP protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the PCIP protein or biologically active portion thereof is determined. Determining the ability of the test compound to modulate the activity of a PCIP protein can be accomplished, for example, by determining the ability of the PCIP protein to bind to a PCIP target molecule by one of the methods described above for determining direct binding. Determining the ability of the PCIP protein to bind to a PCIP target molecule can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA). Sjolander, S. and Urbaniczky, C. (1991) *Anal. Chem.* 63:2338-2345 and Szabo *et al.* (1995) *Curr. Opin. Struct. Biol.* 5:699-705. As used herein, "BIA" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the optical phenomenon of surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

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test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase/ PCIP fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto glutathione sepharose beads

- 5 (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or PCIP protein, and the mixture incubated under conditions conducive to complex formation (e.g., at physiological conditions for salt and pH). Following incubation, the beads or microtitre plate wells are washed to remove any unbound
- 10 components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of PCIP binding or activity determined using standard techniques.

- Other techniques for immobilizing proteins on matrices can also be used in the
- 15 screening assays of the invention. For example, either a PCIP protein or a PCIP target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated PCIP protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well
- 20 plates (Pierce Chemical). Alternatively, antibodies reactive with PCIP protein or target molecules but which do not interfere with binding of the PCIP protein to its target molecule can be derivatized to the wells of the plate, and unbound target or PCIP protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include
- 25 immunodetection of complexes using antibodies reactive with the PCIP protein or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the PCIP protein or target molecule.

- In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate vesicular traffic
- 30 and protein transport in a cell, e.g., a neuronal or cardiac cell, using the assays described in, for example, Komada M. *et al.* (1999) *Genes Dev.*13(11):1475-85, and Roth M.G. *et*

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al. (1999) *Chem. Phys. Lipids*. 98(1-2):141-52, the contents of which are incorporated herein by reference.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to regulate the phosphorylation state of a potassium channel protein or portion thereof, using for example, an *in vitro* kinase assay. Briefly, a PCIP target molecule, *e.g.*, an immunoprecipitated potassium channel from a cell line expressing such a molecule, can be incubated with the PCIP protein and radioactive ATP, *e.g.*, [γ - 32 P] ATP, in a buffer containing MgCl₂ and MnCl₂, *e.g.*, 10 mM MgCl₂ and 5 mM MnCl₂. Following the incubation, the immunoprecipitated PCIP target molecule, *e.g.*, the potassium channel, can be separated by SDS-polyacrylamide gel electrophoresis under reducing conditions, transferred to a membrane, *e.g.*, a PVDF membrane, and autoradiographed. The appearance of detectable bands on the autoradiograph indicates that the PCIP substrate, *e.g.*, the potassium channel, has been phosphorylated. Phosphoaminoacid analysis of the phosphorylated substrate can also be performed in order to determine which residues on the PCIP substrate are phosphorylated. Briefly, the radiophosphorylated protein band can be excised from the SDS gel and subjected to partial acid hydrolysis. The products can then be separated by one-dimensional electrophoresis and analyzed on, for example, a phosphoimager and compared to ninhydrin-stained phosphoaminoacid standards.

Assays such as those described in, for example, Tamaskovic R. *et al.* (1999) *Biol. Chem.* 380(5):569-78, the contents of which are incorporated herein by reference, can also be used.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to associate with (e.g., bind) calcium, using for example, the assays described in Liu L. (1999) *Cell Signal.* 11(5):317-24 and Kawai T. *et al.* (1999) *Oncogene* 18(23):3471-80, the contents of which are incorporated herein by reference.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate chromatin formation in a cell, using for example, the assays described in Okuwaki M. *et*

al. (1998) *J. Biol. Chem.* 273(51):34511-8 and Miyaji-Yamaguchi M. (1999) *J. Mol. Biol.* 290(2): 547-557, the contents of which are incorporated herein by reference.

In yet another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate

- 5 cellular proliferation, using for example, the assays described in Baker F.L. *et al.* (1995) *Cell Prolif.* 28(1):1-15, Cheviron N. *et al.* (1996) *Cell Prolif.* 29(8):437-46, Hu Z.W. *et al.* (1999) *J. Pharmacol. Exp. Ther.* 290(1):28-37 and Elliott K. *et al.* (1999) *Oncogene* 18(24):3564-73, the contents of which are incorporated herein by reference.

- 10 In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to regulate the association of a potassium channel protein or portion thereof with the cellular cytoskeleton, using for example, the assays described in Gonzalez C. *et al.* (1998) *Cell Mol. Biol.* 44(7):1117-27 and Chia C.P. *et al.* (1998) *Exp. Cell Res.* 244(1):340-8, the contents of which are incorporated herein by reference.

- 15 In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate membrane excitability, using for example, the assays described in Bar-Sagi D. *et al.* (1985) *J. Biol. Chem.* 260(8):4740-4 and Barker J.L. *et al.* (1984) *Neurosci. Lett.* 47(3):313-8, the contents of which are incorporated herein by reference.

- 20 In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate cytokine signaling in a cell, *e.g.*, a neuronal or cardiac cell, the assays described in Nakashima Y. *et al.* (1999) *J. Bone Joint Surg. Am.* 81(5):603-15, the contents of which are incorporated herein by reference.

- 25 In another embodiment, modulators of PCIP expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of PCIP mRNA or protein in the cell is determined. The level of expression of PCIP mRNA or protein in the presence of the candidate compound is compared to the level of expression of PCIP mRNA or protein in the absence of the candidate compound. The
30 candidate compound can then be identified as a modulator of PCIP expression based on this comparison. For example, when expression of PCIP mRNA or protein is greater

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(statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of PCIP mRNA or protein expression. Alternatively, when expression of PCIP mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of PCIP mRNA or protein expression. The level of PCIP mRNA or protein expression in the cells can be determined by methods described herein for detecting PCIP mRNA or protein.

- In yet another aspect of the invention, the PCIP proteins can be used as "bait proteins" in a two-hybrid assay or three-hybrid assay (see, *e.g.*, U.S. Patent No. 5,283,317; Zervos *et al.* (1993) *Cell* 72:223-232; Madura *et al.* (1993) *J. Biol. Chem.* 268:12046-12054; Bartel *et al.* (1993) *Biotechniques* 14:920-924; Iwabuchi *et al.* (1993) *Oncogene* 8:1693-1696; and Brent WO94/10300), to identify other proteins, which bind to or interact with PCIP ("PCIP-binding proteins" or "PCIP-bp") and are involved in PCIP activity (described in more detail in the Examples section below).
- Such PCIP-binding proteins are also likely to be involved in the propagation of signals by the PCIP proteins or PCIP targets as, for example, downstream elements of a PCIP-mediated signaling pathway. Alternatively, such PCIP-binding proteins are likely to be PCIP inhibitors.

- The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for a PCIP protein is fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming a PCIP-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies

containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the PCIP protein.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a PCIP modulating agent, an antisense PCIP nucleic acid molecule, a PCIP-specific antibody, or a PCIP-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments, *e.g.*, treatments of a CNS disorder or a cardiovascular disorder, as described herein.

15 B. Detection Assays

Portions or fragments of the cDNA sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome; and, thus, locate gene regions associated with genetic disease; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample. These applications are described in the subsections below.

25 1. Chromosome Mapping

Once the sequence (or a portion of the sequence) of a gene has been isolated, this sequence can be used to map the location of the gene on a chromosome. This process is called chromosome mapping. Accordingly, portions or fragments of the PCIP nucleotide sequences, described herein, can be used to map the location of the PCIP genes on a chromosome. The mapping of the PCIP sequences to chromosomes is an important first step in correlating these sequences with genes associated with disease.

Briefly, PCIP genes can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp in length) from the PCIP nucleotide sequences. Computer analysis of the PCIP sequences can be used to predict primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers can then be used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the PCIP sequences will yield an amplified fragment.

Somatic cell hybrids are prepared by fusing somatic cells from different mammals (e.g., human and mouse cells). As hybrids of human and mouse cells grow and divide, they gradually lose human chromosomes in random order, but retain the mouse chromosomes. By using media in which mouse cells cannot grow, because they lack a particular enzyme, but human cells can, the one human chromosome that contains the gene encoding the needed enzyme, will be retained. By using various media, panels of hybrid cell lines can be established. Each cell line in a panel contains either a single human chromosome or a small number of human chromosomes, and a full set of mouse chromosomes, allowing easy mapping of individual genes to specific human chromosomes. (D'Eustachio P. *et al.* (1983) *Science* 220:919-924). Somatic cell hybrids containing only fragments of human chromosomes can also be produced by using human chromosomes with translocations and deletions.

PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular sequence to a particular chromosome. Three or more sequences can be assigned per day using a single thermal cycler. Using the PCIP nucleotide sequences to design oligonucleotide primers, sublocalization can be achieved with panels of fragments from specific chromosomes. Other mapping strategies which can similarly be used to map a PCIP sequence to its chromosome include *in situ* hybridization (described in Fan, Y. *et al.* (1990) *Proc. Natl. Acad. Sci. USA*, 87:6223-27), pre-screening with labeled flow-sorted chromosomes, and pre-selection by hybridization to chromosome specific cDNA libraries.

Fluorescence *in situ* hybridization (FISH) of a DNA sequence to a metaphase chromosomal spread can further be used to provide a precise chromosomal location in one step. Chromosome spreads can be made using cells whose division has been

blocked in metaphase by a chemical such as colcemid that disrupts the mitotic spindle. The chromosomes can be treated briefly with trypsin, and then stained with Giemsa. A pattern of light and dark bands develops on each chromosome, so that the chromosomes can be identified individually. The FISH technique can be used with a DNA sequence as short as 500 or 600 bases. However, clones larger than 1,000 bases have a higher likelihood of binding to a unique chromosomal location with sufficient signal intensity for simple detection. Preferably 1,000 bases, and more preferably 2,000 bases will suffice to get good results at a reasonable amount of time. For a review of this technique, see Verma *et al.*, Human Chromosomes: A Manual of Basic Techniques (Pergamon Press, New York 1988).

Reagents for chromosome mapping can be used individually to mark a single chromosome or a single site on that chromosome, or panels of reagents can be used for marking multiple sites and/or multiple chromosomes. Reagents corresponding to noncoding regions of the genes actually are preferred for mapping purposes. Coding sequences are more likely to be conserved within gene families, thus increasing the chance of cross hybridizations during chromosomal mapping.

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. (Such data are found, for example, in V. McKusick, Mendelian Inheritance in Man, available on-line through Johns Hopkins University Welch Medical Library). The relationship between a gene and a disease, mapped to the same chromosomal region, can then be identified through linkage analysis (co-inheritance of physically adjacent genes), described in, for example, Egeland, J. *et al.* (1987) *Nature*, 325:783-787.

Moreover, differences in the DNA sequences between individuals affected and unaffected with a disease associated with the PCIP gene, can be determined. If a mutation is observed in some or all of the affected individuals but not in any unaffected individuals, then the mutation is likely to be the causative agent of the particular disease. Comparison of affected and unaffected individuals generally involves first looking for structural alterations in the chromosomes, such as deletions or translocations that are visible from chromosome spreads or detectable using PCR based on that DNA sequence.

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Ultimately, complete sequencing of genes from several individuals can be performed to confirm the presence of a mutation and to distinguish mutations from polymorphisms.

2. Tissue Typing

5 The PCIP sequences of the present invention can also be used to identify individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield
10 unique bands for identification. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The sequences of the present invention are useful as additional DNA markers for RFLP (described in U.S. Patent 5,272,057).

 Furthermore, the sequences of the present invention can be used to provide an
15 alternative technique which determines the actual base-by-base DNA sequence of selected portions of an individual's genome. Thus, the PCIP nucleotide sequences described herein can be used to prepare two PCR primers from the 5' and 3' ends of the sequences. These primers can then be used to amplify an individual's DNA and subsequently sequence it.

20 Panels of corresponding DNA sequences from individuals, prepared in this manner, can provide unique individual identifications, as each individual will have a unique set of such DNA sequences due to allelic differences. The sequences of the present invention can be used to obtain such identification sequences from individuals and from tissue. The PCIP nucleotide sequences of the invention uniquely represent
25 portions of the human genome. Allelic variation occurs to some degree in the coding regions of these sequences, and to a greater degree in the noncoding regions. It is estimated that allelic variation between individual humans occurs with a frequency of about once per each 500 bases. Each of the sequences described herein can, to some degree, be used as a standard against which DNA from an individual can be compared
30 for identification purposes. Because greater numbers of polymorphisms occur in the noncoding regions, fewer sequences are necessary to differentiate individuals. Non-

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coding sequences can comfortably provide positive individual identification with a panel of perhaps 10 to 1,000 primers which each yield a noncoding amplified sequence of 100 bases. If predicted coding sequences are used, a more appropriate number of primers for positive individual identification would be 500-2,000.

- 5 If a panel of reagents from PCIP nucleotide sequences described herein is used to generate a unique identification database for an individual, those same reagents can later be used to identify tissue from that individual. Using the unique identification database, positive identification of the individual, living or dead, can be made from extremely small tissue samples.

10

3. Use of Partial PCIP Sequences in Forensic Biology

- DNA-based identification techniques can also be used in forensic biology. Forensic biology is a scientific field employing genetic typing of biological evidence found at a crime scene as a means for positively identifying, for example, a perpetrator of a crime. To make such an identification, PCR technology can be used to amplify DNA sequences taken from very small biological samples such as tissues, *e.g.*, hair or skin, or body fluids, *e.g.*, blood, saliva, or semen found at a crime scene. The amplified sequence can then be compared to a standard, thereby allowing identification of the origin of the biological sample.

- 20 The sequences of the present invention can be used to provide polynucleotide reagents, *e.g.*, PCR primers, targeted to specific loci in the human genome, which can enhance the reliability of DNA-based forensic identifications by, for example, providing another "identification marker" (*i.e.* another DNA sequence that is unique to a particular individual). As mentioned above, actual base sequence information can be used for
- 25 identification as an accurate alternative to patterns formed by restriction enzyme generated fragments. Sequences targeted to noncoding regions are particularly appropriate for this use as greater numbers of polymorphisms occur in the noncoding regions, making it easier to differentiate individuals using this technique. Examples of polynucleotide reagents include the PCIP nucleotide sequences or portions thereof,
- 30 having a length of at least 20 bases, preferably at least 30 bases.

The PCIP nucleotide sequences described herein can further be used to provide polynucleotide reagents, *e.g.*, labeled or labelable probes which can be used in, for example, an *in situ* hybridization technique, to identify a specific tissue, *e.g.*, brain tissue. This can be very useful in cases where a forensic pathologist is presented with a
5 tissue of unknown origin. Panels of such PCIP probes can be used to identify tissue by species and/or by organ type.

In a similar fashion, these reagents, *e.g.*, PCIP primers or probes can be used to screen tissue culture for contamination (*i.e.* screen for the presence of a mixture of different types of cells in a culture).

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C. Predictive Medicine:

The present invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically.
15 Accordingly, one aspect of the present invention relates to diagnostic assays for determining PCIP protein and/or nucleic acid expression as well as PCIP activity, in the context of a biological sample (*e.g.*, blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a disease or disorder, or is at risk of developing a disorder, associated with aberrant PCIP expression or activity. The invention also
20 provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder associated with PCIP protein, nucleic acid expression or activity. For example, mutations in a PCIP gene can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a disorder characterized by or associated with
25 PCIP protein, nucleic acid expression or activity.

Another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs, compounds) on the expression or activity of PCIP in clinical trials.

These and other agents are described in further detail in the following sections.

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1. Diagnostic Assays

An exemplary method for detecting the presence or absence of PCIP protein or nucleic acid in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of

5 detecting PCIP protein or nucleic acid (*e.g.*, mRNA, genomic DNA) that encodes PCIP protein such that the presence of PCIP protein or nucleic acid is detected in the biological sample. A preferred agent for detecting PCIP mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to PCIP mRNA or genomic DNA. The nucleic acid probe can be, for example, a full-length PCIP nucleic acid, such as the

10 nucleic acid of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID

15 NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and

20 sufficient to specifically hybridize under stringent conditions to PCIP mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

A preferred agent for detecting PCIP protein is an antibody capable of binding to PCIP protein, preferably an antibody with a detectable label. Antibodies can be

25 polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or F(ab')₂) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is

30 directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with

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biotin such that it can be detected with fluorescently labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. That is, the detection method of the invention can be used to detect PCIP mRNA, protein, or

5 genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of PCIP mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of PCIP protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of PCIP genomic DNA include

10 Southern hybridizations. Furthermore, *in vivo* techniques for detection of PCIP protein include introducing into a subject a labeled anti-PCIP antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

In one embodiment, the biological sample contains protein molecules from the

15 test subject. Alternatively, the biological sample can contain mRNA molecules from the test subject or genomic DNA molecules from the test subject. A preferred biological sample is a serum sample or cerebrospinal fluid isolated by conventional means from a subject.

In another embodiment, the methods further involve obtaining a control

20 biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting PCIP protein, mRNA, or genomic DNA, such that the presence of PCIP protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of PCIP protein, mRNA or genomic DNA in the control sample with the presence of PCIP protein, mRNA or genomic DNA in the test

25 sample.

The invention also encompasses kits for detecting the presence of PCIP in a biological sample. For example, the kit can comprise a labeled compound or agent capable of detecting PCIP protein or mRNA in a biological sample; means for determining the amount of PCIP in the sample; and means for comparing the amount of

30 PCIP in the sample with a standard. The compound or agent can be packaged in a

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suitable container. The kit can further comprise instructions for using the kit to detect PCIP protein or nucleic acid.

2. Prognostic Assays

- 5 The diagnostic methods described herein can furthermore be utilized to identify subjects having or at risk of developing a disease or disorder associated with aberrant PCIP expression or activity. For example, the assays described herein, such as the preceding diagnostic assays or the following assays, can be utilized to identify a subject having or at risk of developing a disorder associated with a misregulation in PCIP
- 10 protein activity or nucleic acid expression, such as a neurodegenerative disorder, *e.g.*, Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, spinocerebellar ataxia, and Jakob-Creutzfeldt disease; a psychiatric disorder, *e.g.*, depression, schizophrenic
- 15 disorders, Korsakoff's psychosis, mania, anxiety disorders, bipolar affective disorders, or phobic disorders; a learning or memory disorder, *e.g.*, amnesia or age-related memory loss; a neurological disorder, *e.g.*, migraine; a pain disorder, *e.g.*, hyperalgesia or pain associated with musculoskeletal disorders; spinal cord injury; stroke; and head trauma; or a cardiovascular disorder, *e.g.*, sinus node dysfunction, angina, heart failure,
- 20 hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrhythmia.

- Alternatively, the prognostic assays can be utilized to identify a subject having or at risk for developing a disorder associated with a misregulation in PCIP protein activity
- 25 or nucleic acid expression, such as a potassium channel associated disorder. Thus, the present invention provides a method for identifying a disease or disorder associated with aberrant PCIP expression or activity in which a test sample is obtained from a subject and PCIP protein or nucleic acid (*e.g.*, mRNA or genomic DNA) is detected, wherein the presence of PCIP protein or nucleic acid is diagnostic for a subject having or at risk
- 30 of developing a disease or disorder associated with aberrant PCIP expression or activity. As used herein, a "test sample" refers to a biological sample obtained from a subject of

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interest. For example, a test sample can be a biological fluid (*e.g.*, serum), cell sample, or tissue.

Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) to treat a disease or disorder associated with aberrant PCIP expression or activity. For example, such methods can be used to determine whether a subject can be effectively treated with an agent for a CNS disorder or a cardiovascular disorder. Thus, the present invention provides methods for determining whether a subject can be effectively treated with an agent for a disorder associated with aberrant PCIP expression or activity in which a test sample is obtained and PCIP protein or nucleic acid expression or activity is detected (*e.g.*, wherein the abundance of PCIP protein or nucleic acid expression or activity is diagnostic for a subject that can be administered the agent to treat a disorder associated with aberrant PCIP expression or activity).

The methods of the invention can also be used to detect genetic alterations in a PCIP gene, thereby determining if a subject with the altered gene is at risk for a disorder characterized by misregulation in PCIP protein activity or nucleic acid expression, such as a CNS disorder or a cardiovascular disorder. In preferred embodiments, the methods include detecting, in a sample of cells from the subject, the presence or absence of a genetic alteration characterized by at least one of an alteration affecting the integrity of a gene encoding a PCIP-protein, or the mis-expression of the PCIP gene. For example, such genetic alterations can be detected by ascertaining the existence of at least one of 1) a deletion of one or more nucleotides from a PCIP gene; 2) an addition of one or more nucleotides to a PCIP gene; 3) a substitution of one or more nucleotides of a PCIP gene, 4) a chromosomal rearrangement of a PCIP gene; 5) an alteration in the level of a messenger RNA transcript of a PCIP gene, 6) aberrant modification of a PCIP gene, such as of the methylation pattern of the genomic DNA, 7) the presence of a non-wild type splicing pattern of a messenger RNA transcript of a PCIP gene, 8) a non-wild type level of a PCIP-protein, 9) allelic loss of a PCIP gene, and 10) inappropriate post-translational modification of a PCIP-protein. As described herein, there are a large number of assays known in the art which can be used for detecting alterations in a PCIP

gene. A preferred biological sample is a tissue or serum sample isolated by conventional means from a subject.

In certain embodiments, detection of the alteration involves the use of a probe/primer in a polymerase chain reaction (PCR) (see, e.g., U.S. Patent Nos.

- 5 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, e.g., Landegran *et al.* (1988) *Science* 241:1077-1080; and Nakazawa *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:360-364), the latter of which can be particularly useful for detecting point mutations in the PCIP-gene (see Abravaya *et al.* (1995) *Nucleic Acids Res.* 23:675-682). This method can include the steps of
- 10 collecting a sample of cells from a subject, isolating nucleic acid (e.g., genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a PCIP gene under conditions such that hybridization and amplification of the PCIP-gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the
- 15 amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

- Alternative amplification methods include: self sustained sequence replication (Guatelli, J.C. *et al.*, (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional
- 20 amplification system (Kwoh, D.Y. *et al.*, (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi, P.M. *et al.* (1988) *Bio-Technology* 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such
 - 25 molecules are present in very low numbers.

- In an alternative embodiment, mutations in a PCIP gene from a sample cell can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel
- 30 electrophoresis and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence

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specific ribozymes (see, for example, U.S. Patent No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

- In other embodiments, genetic mutations in PCIP can be identified by
- 5 hybridizing a sample and control nucleic acids, e.g., DNA or RNA, to high density arrays containing hundreds or thousands of oligonucleotides probes (Cronin, M.T. *et al.* (1996) *Human Mutation* 7: 244-255; Kozal, M.J. *et al.* (1996) *Nature Medicine* 2: 753-759). For example, genetic mutations in PCIP can be identified in two dimensional arrays containing light-generated DNA probes as described in Cronin, M.T. *et al. supra*.
 - 10 Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential overlapping probes. This step allows the identification of point mutations. This step is followed by a second hybridization array that allows the characterization of specific mutations by using smaller, specialized probe
 - 15 arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

- In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the PCIP gene and detect mutations by
- 20 comparing the sequence of the sample PCIP with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxam and Gilbert ((1977) *Proc. Natl. Acad. Sci. USA* 74:560) or Sanger ((1977) *Proc. Natl. Acad. Sci. USA* 74:5463). It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the
 - 25 diagnostic assays ((1995) *Biotechniques* 19:448), including sequencing by mass spectrometry (see, e.g., PCT International Publication No. WO 94/16101; Cohen *et al.* (1996) *Adv. Chromatogr.* 36:127-162; and Griffin *et al.* (1993) *Appl. Biochem. Biotechnol.* 38:147-159).

- Other methods for detecting mutations in the PCIP gene include methods in
- 30 which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes (Myers *et al.* (1985) *Science* 230:1242). In general, the

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- art technique of "mismatch cleavage" starts by providing heteroduplexes of formed by hybridizing (labeled) RNA or DNA containing the wild-type PCIP sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent which cleaves single-stranded regions of the duplex
- 5 such as which will exist due to basepair mismatches between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S1 nuclease to enzymatically digesting the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched
- 10 regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. See, for example, Cotton *et al.* (1988) *Proc. Natl Acad Sci USA* 85:4397; Saleeba *et al.* (1992) *Methods Enzymol.* 217:286-295. In a preferred embodiment, the control DNA or RNA can be labeled for detection.
- 15 In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in PCIP cDNAs obtained from samples of cells. For example, the mutY enzyme of *E. coli* cleaves A at G/A mismatches and the thymidine DNA glycosylase
- 20 from HeLa cells cleaves T at G/T mismatches (Hsu *et al.* (1994) *Carcinogenesis* 15:1657-1662). According to an exemplary embodiment, a probe based on a PCIP sequence, *e.g.*, a wild-type PCIP sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the
- 25 like. See, for example, U.S. Patent No. 5,459,039.

In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in PCIP genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita *et al.* (1989) *Proc Natl. Acad. Sci*

30 *USA*: 86:2766, see also Cotton (1993) *Mutat. Res.* 285:125-144; and Hayashi (1992) *Genet. Anal. Tech. Appl.* 9:73-79). Single-stranded DNA fragments of sample and

control PCIP nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In a preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen *et al.* (1991) *Trends Genet* 7:5).

In yet another embodiment the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers *et al.* (1985) *Nature* 313:495). When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) *Biophys Chem* 265:12753).

Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki *et al.* (1986) *Nature* 324:163); Saiki *et al.* (1989) *Proc. Natl Acad. Sci USA* 86:6230). Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA.

Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs *et al.* (1989) *Nucleic Acids Res.* 17:2437-2448) or at the extreme 3'

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end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) *Tibtech* 11:238). In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini *et al.* (1992) *Mol. Cell Probes* 6:1). It is anticipated that in certain

5 embodiments amplification may also be performed using Taq ligase for amplification (Barany (1991) *Proc. Natl. Acad. Sci USA* 88:189). In such cases, ligation will occur only if there is a perfect match at the 3' end of the 5' sequence making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

10 The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits comprising at least one probe nucleic acid or antibody reagent described herein, which may be conveniently used, *e.g.*, in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness involving a PCIP gene.

15 Furthermore, any cell type or tissue in which PCIP is expressed may be utilized in the prognostic assays described herein.

3. Monitoring of Effects During Clinical Trials

Monitoring the influence of agents (*e.g.*, drugs) on the expression or activity of a

20 PCIP protein (*e.g.*, the modulation of membrane excitability or resting potential) can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent determined by a screening assay as described herein to increase PCIP gene expression, protein levels, or upregulate PCIP activity, can be monitored in clinical trials of subjects exhibiting decreased PCIP gene expression, protein levels, or

25 downregulated PCIP activity. Alternatively, the effectiveness of an agent determined by a screening assay to decrease PCIP gene expression, protein levels, or downregulate PCIP activity, can be monitored in clinical trials of subjects exhibiting increased PCIP gene expression, protein levels, or upregulated PCIP activity. In such clinical trials, the expression or activity of a PCIP gene, and preferably, other genes that have been

30 implicated in, for example, a potassium channel associated disorder can be used as a "read out" or markers of the phenotype of a particular cell.

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For example, and not by way of limitation, genes, including PCIP, that are modulated in cells by treatment with an agent (*e.g.*, compound, drug or small molecule) which modulates PCIP activity (*e.g.*, identified in a screening assay as described herein) can be identified. Thus, to study the effect of agents on potassium channel associated disorders, for example, in a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of PCIP and other genes implicated in the potassium channel associated disorder, respectively. The levels of gene expression (*e.g.*, a gene expression pattern) can be quantified by northern blot analysis or RT-PCR, as described herein, or alternatively by measuring the amount of protein produced, by one of the methods as described herein, or by measuring the levels of activity of PCIP or other genes. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the cells to the agent. Accordingly, this response state may be determined before, and at various points during treatment of the individual with the agent.

In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate identified by the screening assays described herein) including the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of a PCIP protein, mRNA, or genomic DNA in the preadministration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression or activity of the PCIP protein, mRNA, or genomic DNA in the post-administration samples; (v) comparing the level of expression or activity of the PCIP protein, mRNA, or genomic DNA in the pre-administration sample with the PCIP protein, mRNA, or genomic DNA in the post administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of PCIP to higher levels than detected, *i.e.*, to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of PCIP to lower levels than detected, *i.e.* to decrease the effectiveness of the agent. According to such an

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embodiment, PCIP expression or activity may be used as an indicator of the effectiveness of an agent, even in the absence of an observable phenotypic response.

D. Methods of Treatment:

- 5 The present invention provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated with aberrant PCIP expression or activity. With regards to both prophylactic and therapeutic methods of treatment, such treatments may be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics.
- 10 "Pharmacogenomics", as used herein, refers to the application of genomics technologies such as gene sequencing, statistical genetics, and gene expression analysis to drugs in clinical development and on the market. More specifically, the term refers the study of how a patient's genes determine his or her response to a drug (*e.g.*, a patient's "drug response phenotype", or "drug response genotype".) Thus, another aspect of the
- 15 invention provides methods for tailoring an individual's prophylactic or therapeutic treatment with either the PCIP molecules of the present invention or PCIP modulators according to that individual's drug response genotype. Pharmacogenomics allows a clinician or physician to target prophylactic or therapeutic treatments to patients who will most benefit from the treatment and to avoid treatment of patients who will
- 20 experience toxic drug-related side effects.

1. Prophylactic Methods

- In one aspect, the invention provides a method for preventing in a subject, a disease or condition associated with an aberrant PCIP expression or activity, by
- 25 administering to the subject a PCIP or an agent which modulates PCIP expression or at least one PCIP activity. Subjects at risk for a disease which is caused or contributed to by aberrant PCIP expression or activity can be identified by, for example, any or a combination of diagnostic or prognostic assays as described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of the
- 30 PCIP aberrancy, such that a disease or disorder is prevented or, alternatively, delayed in its progression. Depending on the type of PCIP aberrancy, for example, a PCIP, PCIP

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agonist or PCIP antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein.

2. Therapeutic Methods

5 Another aspect of the invention pertains to methods of modulating PCIP expression or activity for therapeutic purposes. Accordingly, in an exemplary embodiment, the modulatory method of the invention involves contacting a cell with a PCIP or agent that modulates one or more of the activities of PCIP protein activity associated with the cell. An agent that modulates PCIP protein activity can be an agent
10 as described herein, such as a nucleic acid or a protein, a naturally-occurring target molecule of a PCIP protein (*e.g.*, a PCIP substrate), a PCIP antibody, a PCIP agonist or antagonist, a peptidomimetic of a PCIP agonist or antagonist, or other small molecule. In one embodiment, the agent stimulates one or more PCIP activities. Examples of such stimulatory agents include active PCIP protein and a nucleic acid molecule encoding
15 PCIP that has been introduced into the cell. In another embodiment, the agent inhibits one or more PCIP activities. Examples of such inhibitory agents include antisense PCIP nucleic acid molecules, anti-PCIP antibodies, and PCIP inhibitors. These modulatory methods can be performed *in vitro* (*e.g.*, by culturing the cell with the agent) or, alternatively, *in vivo* (*e.g.*, by administering the agent to a subject). As such, the present
20 invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant expression or activity of a PCIP protein or nucleic acid molecule. Examples of such disorders include CNS disorders such as neurodegenerative disorders, *e.g.*, Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis,
25 amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, and Jakob-Creutzfeldt disease; psychiatric disorders, *e.g.*, depression, schizophrenic disorders, Korsakoff's psychosis, mania, anxiety disorders, bipolar affective disorders, or phobic disorders; learning or memory disorders, *e.g.*, amnesia or age-related memory loss; neurological disorders, *e.g.*, migraine; pain disorders, *e.g.*, hyperalgesia or pain
30 associated with musculoskeletal disorders; spinal cord injury; stroke; and head trauma; or cardiovascular disorders, *e.g.*, arteriosclerosis, ischemia reperfusion injury, restenosis,

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- arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, atrial fibrillation, long-QT syndrome, congestive heart failure, sinus node dysfunction, angina,
- 5 heart failure, hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrhythmia. In one embodiment, the method involves administering an agent (*e.g.*, an agent identified by a screening assay described herein), or combination of agents that modulates (*e.g.*, upregulates or downregulates) PCIP expression or activity.
- 10 In another embodiment, the method involves administering a PCIP protein or nucleic acid molecule as therapy to compensate for reduced or aberrant PCIP expression or activity.

- A preferred embodiment of the present invention involves a method for treatment of a PCIP associated disease or disorder which includes the step of administering a
- 15 therapeutically effective amount of a PCIP antibody to a subject. As defined herein, a therapeutically effective amount of antibody (*i.e.*, an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight, and even more preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight. The
- 20 skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of an antibody can include a single treatment or, preferably, can include a series
- 25 of treatments. In a preferred example, a subject is treated with antibody in the range of between about 0.1 to 20 mg/kg body weight, one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated that the effective dosage of antibody used for treatment may increase or decrease over
- 30 the course of a particular treatment. Changes in dosage may result from the results of diagnostic assays as described herein.

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Stimulation of PCIP activity is desirable in situations in which PCIP is abnormally downregulated and/or in which increased PCIP activity is likely to have a beneficial effect. For example, stimulation of PCIP activity is desirable in situations in which a PCIP is downregulated and/or in which increased PCIP activity is likely to have a beneficial effect. Likewise, inhibition of PCIP activity is desirable in situations in which PCIP is abnormally upregulated and/or in which decreased PCIP activity is likely to have a beneficial effect.

3. Pharmacogenomics

The PCIP molecules of the present invention, as well as agents, or modulators which have a stimulatory or inhibitory effect on PCIP activity (*e.g.*, PCIP gene expression) as identified by a screening assay described herein can be administered to individuals to treat (prophylactically or therapeutically) potassium channel associated disorders associated with aberrant PCIP activity (*e.g.*, CNS disorders such as neurodegenerative disorders, *e.g.*, Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, spinocerebellar ataxia, and Jakob-Creutzfeldt disease; psychiatric disorders, *e.g.*, depression, schizophrenic disorders, Korsakoff's psychosis, mania, anxiety disorders, bipolar affective disorders, or phobic disorders; learning or memory disorders, *e.g.*, amnesia or age-related memory loss; neurological disorders, *e.g.*, migraine; pain disorders, *e.g.*, hyperalgesia or pain associated with musculoskeletal disorders; spinal cord injury; stroke; and head trauma; or cardiovascular disorders such as arteriosclerosis, ischemia reperfusion injury, restenosis, arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, atrial fibrillation, long-QT syndrome, congestive heart failure, sinus node disfunction, angina, heart failure, hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrhythmia). In conjunction with such treatment, pharmacogenomics (*i.e.*, the study of the relationship between an individual's genotype

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and that individual's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician may consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a PCIP molecule or PCIP modulator as well as tailoring the dosage and/or therapeutic regimen of treatment with a PCIP molecule or PCIP modulator.

Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, for example, Eichelbaum, M. *et al.* (1996) *Clin. Exp. Pharmacol. Physiol.* 23(10-11):983-985 and Linder, M.W. *et al.* (1997) *Clin. Chem.* 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur either as rare genetic defects or as naturally-occurring polymorphisms. For example, glucose-6-phosphate dehydrogenase deficiency (G6PD) is a common inherited enzymopathy in which the main clinical complication is haemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

One pharmacogenomics approach to identifying genes that predict drug response, known as "a genome-wide association", relies primarily on a high-resolution map of the human genome consisting of already known gene-related markers (*e.g.*, a "bi-allelic" gene marker map which consists of 60,000-100,000 polymorphic or variable sites on the human genome, each of which has two variants.) Such a high-resolution genetic map can be compared to a map of the genome of each of a statistically significant number of patients taking part in a Phase II/III drug trial to identify markers associated with a particular observed drug response or side effect. Alternatively, such a high resolution map can be generated from a combination of some ten-million known single nucleotide polymorphisms (SNPs) in the human genome. As used herein, a "SNP" is a common alteration that occurs in a single nucleotide base in a stretch of

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DNA. For example, a SNP may occur once per every 1000 bases of DNA. A SNP may be involved in a disease process, however, the vast majority may not be disease-associated. Given a genetic map based on the occurrence of such SNPs, individuals can be grouped into genetic categories depending on a particular pattern of SNPs in their individual genome. In such a manner, treatment regimens can be tailored to groups of genetically similar individuals, taking into account traits that may be common among such genetically similar individuals.

Alternatively, a method termed the "candidate gene approach", can be utilized to identify genes that predict drug response. According to this method, if a gene that encodes a drugs target is known (*e.g.*, a PCIP protein of the present invention), all common variants of that gene can be fairly easily identified in the population and it can be determined if having one version of the gene versus another is associated with a particular drug response.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

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Alternatively, a method termed the "gene expression profiling", can be utilized to identify genes that predict drug response. For example, the gene expression of an animal dosed with a drug (*e.g.*, a PCIP molecule or PCIP modulator of the present invention) can give an indication whether gene pathways related to toxicity have been turned on.

Information generated from more than one of the above pharmacogenomics approaches can be used to determine appropriate dosage and treatment regimens for prophylactic or therapeutic treatment an individual. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a PCIP molecule or PCIP modulator, such as a modulator identified by one of the exemplary screening assays described herein.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application, as well as the Figures and the Sequence Listing are incorporated herein by reference.

EXAMPLES

The following materials and methods were used in the Examples.

Strains, plasmids, bait cDNAs, and general microbiological techniques

Basic yeast strains (HF7c, Y187,) bait (pGBT9) and fish (pACT2) plasmids used in this work were purchased from Clontech (Palo Alto, CA). cDNAs encoding rat Kv4.3, Kv4.2, and Kv1.1, were provided by Wyeth-Ayerst Research (865 Ridge Rd., Monmouth Junction, NJ 08852) Standard yeast media including synthetic complete medium lacking L-leucine, L-tryptophan, and L-histidine were prepared and yeast genetic manipulations were performed as described (Sherman (1991) *Meth. Enzymol.* 194:3-21). Yeast transformations were performed using standard protocols (Gietz *et al.* (1992) *Nucleic Acids Res.* 20:1425; Ito *et al* (1983) *J. Bacteriol.* 153:163-168). Plasmid

DNAs were isolated from yeast strains by a standard method (Hoffman and Winston (1987) *Gene* 57:267-272).

Bait and Yeast Strain Construction

- 5 The first 180 amino acids of rKv4.3 (described in Serdio P. *et al.* (1996) *J. Neurophys* 75:2174-2179) were amplified by PCR and cloned in frame into pGBT9 resulting in plasmid pFWA2, (hereinafter "bait"). This bait was transformed into the two-hybrid screening strain HF7c and tested for expression and self-activation. The bait was validated for expression by Western blotting. The rKv4.3 bait did not self-activate
- 10 in the presence of 10 mM 3-amino-1,2,3-Triazole (3-AT).

Library construction

- Rat mid brain tissue was provided by Wyeth-Ayerst Research (Monmouth Junction, NJ). Total cellular RNA was extracted from the tissues using standard
- 15 techniques (Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual*. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1989)). mRNA was prepared using a Poly-A Spin mRNA Isolation Kit from New England Biolabs (Beverly, MA). cDNA from the mRNA sample was synthesized using a cDNA Synthesis Kit from Stratagene (La
- 20 Jolla, CA) and ligated into pACT2's EcoRI and XhoI sites, giving rise to a two-hybrid library.

Two-Hybrid Screening

- Two-hybrid screens were carried out essentially as described in Bartel, P. *et al.*
- 25 (1993) "Using the Two-Hybrid System to Detect Polypeptide-Polypeptide Interactions" in *Cellular Interactions in Development: A Practical Approach*, Hartley, D.A. ed. Oxford University Press, Oxford, pp. 153-179, with a bait-library pair of rkv4.3 bait-rat mid brain library. A filter disk beta-galactosidase (beta-gal) assay was performed essentially as previously described (Brill *et al.* (1994) *Mol. Biol. Cell.* 5:297-312). Clones that were
- 30 positive for both reporter gene activity (His and beta-galactosidase) were scored and fish, plasmids were isolated from yeast, transformed into *E. coli* strain KC8, DNA

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5 Positive interactor clones were subjected to a binding specificity test where they were exposed to a panel of related and unrelated baits by a mating scheme previously described (Finley R.L. Jr. *et al.* (1994) *PNAS*, 91(26):12980-12984). Briefly, positive fish plasmids were transformed into Y187 and the panel of baits were transformed into HF7c. Transformed fish and bait cells were streaked out as stripes on selective medium
10 plates, mated on YPAD plates, and tested for reporter gene activity.

PCIP nucleotides were analyzed for nucleic acid hits by the BLASTN 1.4.8MP program (Altschul *et al.* (1990) Basic Local Alignment Search Tool. *J. Mol. Biol.* 215: 403-410). PCIP proteins were analyzed for polypeptide hits by the BLASTP 1.4.9MP program.

The Kv4.3 gene coding sequence (coding for the first 180 amino acids) was amplified by PCR and cloned into pGBT9 creating a GAL4 DNA-binding domain-Kv4.3(1-180) gene fusion (plasmid pFWA2). HF7c was transformed with this construct. The resulting strain grew on synthetic complete medium lacking L-tryptophan but not on synthetic complete medium lacking L-tryptophan and L-histidine in the presence of 10mM 3-AT demonstrating that the {GAL4 DNA-binding domain}-
25 {vKv4.3(1-180)} gene fusion does not have intrinsic transcriptional activation activity higher than the threshold allowed by 10mM 3-AT .

In this example, a yeast two-hybrid assay was performed in which a plasmid containing a {GAL4 DNA-binding domain}-rKv4.3(1-180)} gene fusion was introduced into the yeast two-hybrid screening strain HF7c described above. HF7c was then transformed with the rat mid brain two-hybrid library. Approximately six million transformants were obtained and plated in selection medium. Colonies that grew in the

selection medium and expressed the beta-galactosidase reporter gene were further characterized and subjected to retransformation and specificity assays. The retransformation and specificity tests yielded three PCIP clones (rat 1v, 8t, and 9qm) that were able to bind to the Kv4.3 polypeptide.

- 5 The full length sequences for the rat 1v gene, and partial sequences for 8t and 9q genes were derived as follows. The partial rat PCIP sequences were used to prepare probes, which were then used to screen, for example, rat mid brain cDNA libraries. Positive clones were identified, amplified and sequenced using standard techniques, to obtain the full length sequence. Additionally, a rapid amplification of the existing rat
- 10 PCIP cDNA ends (using for example, 5' RACE, by Gibco, BRL) was used to complete the 5' end of the transcript.

EXAMPLE 2: IDENTIFICATION OF HUMAN 1v cDNA

- To obtain the human 1v nucleic acid molecule, a cDNA library made from a
- 15 human hippocampus (Clontech, Palo Alto, CA) was screened under low stringency conditions as follows: Prehybridization for 4 hours at 42°C in Clontech Express Hyb solution, followed by overnight hybridization at 42°C. The probe used was a PCR-generated fragment including nucleotides 49-711 of the rat sequence labeled with ³²P dCTP. The filters were washed 6 times in 2XSSC/0.1% SDS at 55°C. The same
- 20 conditions were used for secondary screening of the positive isolates. Clones thus obtained were sequenced using an ABI automated DNA Sequencing system, and compared to the rat sequences shown in SEQ ID NO:3 as well as to known sequences from the GenBank database. The largest clone from the library screen was subsequently subcloned into pBS-KS+ (Stratagene, La Jolla, CA) for sequence verification. The 515
- 25 base pair clone was determined to represent the human homolog of the 1v gene, encompassing 211 base pairs of 5' UTR and a 304 base pair coding region. To generate the full-length cDNA, 3' RACE was used according to the manufacturers instructions (Clontech Advantage PCR kit).

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EXAMPLE 3: ISOLATION AND CHARACTERIZATION OF 1V SPLICE VARIANTS

The mouse 1v shown in SEQ ID NO:5 and the rat 1vl splice variant shown in SEQ ID NO:7 was isolated using a two-hybrid assay as described in Example 1. The mouse 1vl splice variant shown in SEQ ID NO: 7 was isolated by screening a mouse brain cDNA library, and the rat 1vn splice variant shown in SEQ ID NO:11 was isolated by BLAST searching.

EXAMPLE 4: ISOLATION AND IDENTIFICATION OF 9Q AND OTHER PCIPs

Rat 9ql (SEQ ID NO: 15) was isolated by database mining, rat 9qm (SEQ ID NO: 21) was isolated by a two-hybrid assay, and rat 9qc (SEQ ID NO:27) was identified by database mining. Human 9ql (SEQ ID NO: 13), and human 9qs (SEQ ID NO: 23) were identified as described in Example 2. Mouse 9ql (SEQ ID NO:17), monkey 9qs (SEQ ID NO:25), human p193 (SEQ ID NO:39), rat p19 (SEQ ID NO:33), and mouse p19 (SEQ ID NO:35) were identified by database mining. Rat 8t (SEQ ID NO:29) was identified using a two-hybrid assay. The sequence of W28559 (SEQ ID NO:37) was identified by database mining and sequencing of the identified EST with Genbank Accession Number AI352454. The protein sequence was found to contain a 41 amino acid region with strong homology to 1v, 9ql, and p19 (see alignment in Figure 25). However, downstream of this homologous region the sequence diverges from that of the PCIP family. This sequence could represent a gene which possesses a 41 amino acid domain with homology to a similar domain found in the PCIP family members.

The human genomic 9q sequence (SEQ ID NOs:46 and 47) was isolated by screening a BAC genomic DNA library (Reasearch Genetics) using primers which were designed based on the sequence of the human 9qm cDNA. Two positive clones were identified (448O2 and 721I17) and sequenced.

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EXAMPLE 5: EXPRESSION OF 1V, 8T, AND 9Q mRNA IN RAT TISSUES

Rat and mouse multiple tissue Northern blots (Clontech) were probed with a [32P]-labeled cDNA probe directed at the 5'-untranslated and 5'-coding region of the rat 1v sequence (nucleotides 35-124; SEQ ID NO:3) (this probe is specific for rat 1v and rat 1vl), the 5' coding region of the 8t sequence (nucleotides 1-88; SEQ ID NO:29) (this probe is specific for 8t), or the 5' end of the rat 9qm sequence (nucleotides 1-195; SEQ ID NO:21) (this probe is specific for all 9q isoforms, besides 8t). Blots were hybridized using standard techniques. Northern blots hybridized with the rat 1v probe revealed a single band at 2.3kb only in the lane containing brain RNA, suggesting that 1v expression is brain specific. Northern blots probed with the rat 8t probe revealed a major band at 2.4kb. The rat 8t band was most intense in the lane containing heart RNA and there was also a weaker band in the lane containing brain RNA. Northern blots hybridized with the 9q cDNA probe revealed a major band at 2.5kb and a minor band at over 4kb with predominant expression in brain and heart. The minor band may represent incompletely spliced or processed 9q mRNA. The results from the northern blots further indicated that p19 is expressed predominantly in the heart.

EXAMPLE 6: EXPRESSION OF 1V, 8T, AND 9Q IN BRAIN

Expression of the rat 1v and 8t/9q genes in the brain was examined by *in situ* hybridization histochemistry (ISHH) using [35S]-labeled cRNA probes and a hybridization procedure identical to that described in Rhodes *et al.* (1996) J. Neurosci., 16:4846-4860. Templates for preparing the cRNA probes were generated by standard PCR methods. Briefly, oligonucleotide primers were designed to amplify a fragment of 3'- or 5'-untranslated region of the target cDNA and in addition, add the promoter recognition sequences for T7 and T3 polymerase. Thus, to generate a 300 nucleotide probe directed at the 3'-untranslated region of the 1v mRNA, we used the following primers:

5-TAATACGACTCACTATAGGGACTGGCCATCCTGCTCTCAG-3 (T7, forward, sense; SEQ ID NO:42)

5-ATTAACCTCACTAAAGGGCACTACTGTTTAAGCTCAAG-3 (T3, reverse, antisense; SEQ ID NO:43). The underlined bases correspond to the T7 and T3 promoter sequences. To generate a probe directed at a 325 bp region of 3'-untranslated sequence shared by the 8t and 9q mRNAs, the following primers were used:

- 5 5-TAATACGACTCACTATAGGGCACCTCCCCTCCGGCTGTC-3 (T7, forward, sense; SEQ ID NO:44)
5-ATTAACCTCACTAAAGGGGAGAGCAGCAGCATGGCAGGGT-3 (T3, reverse, antisense; SEQ ID NO:45).

Autoradiograms of rat brain tissue sections processed for ISHH localization of 1v or 8t/9q mRNA expression revealed that 1v mRNA is expressed widely in brain in a pattern consistent with labeling of neurons as opposed to glial or endothelial cells. 1v mRNA is highly expressed in cortical, hippocampal, and striatal interneurons, the reticular nucleus of the thalamus, the medial habenula, and in cerebellar granule cells. 1v mRNA is expressed at moderate levels in midbrain nuclei including the substantia nigra and superior colliculus, in several other thalamic nuclei, and in the medial septal and diagonal band nuclei of the basal forebrain.

Because the probe used to analyze the expression of 8t and 9q hybridizes to a region of the 3'-untranslated region that is identical in the 8t and 9q mRNAs, this probe generates a composite image that reveals that 8t/9q mRNA is expressed widely in brain in a pattern that partly overlaps with that for 1v as described above. However, 8t/9q mRNA is highly expressed in the striatum, hippocampal formation, cerebellar granule cells, and neocortex. 8t/9q mRNA is expressed at moderate levels in the midbrain, thalamus, and brainstem. In many of these areas, 8t/9q mRNA appears to be concentrated in interneurons in addition to principal cells, and in all regions 8t/9q expression appears to be concentrated in neurons as opposed to glial cells.

Single- and double-label immunohistochemistry revealed that the PCIP and Kv4 polypeptides are precisely colocalized in many of the cell types and brain regions where PCIP and Kv4 mRNAs are coexpressed. For example, 9qm colocalized with Kv4.2 in the somata and dendrites of hippocampal granule and pyramidal cells, neurons in the medial habenular nucleus and in cerebellar basket cells, while 1v colocalized with Kv4.3 in layer II neurons of posterior cingulate cortex, hippocampal interneurons, and in a

subset of cerebellar granule cells. Immunoprecipitation analyses indicated that 1v and 9qm are coassociated with Kv4 α -subunits in rat brain membranes.

**EXAMPLE 7: CO-ASSOCIATION OF PCIPs AND Kv4 CHANNELS
IN COS AND CHO CELLS**

COS1 and CHO cells were transiently transfected with individual PCIPs (KChIP1, KChIP2, KChIP3) alone or together with Kv4.2 or Kv4.3 using the lipofectamine plus procedure essentially as described by the manufacturer (Boehringer Mannheim). Forty-eight hours after the transfection, cells were washed, fixed, and processed for immunofluorescent visualization as described previously (Bekele-Arcuri *et al.* (1996) *Neuropharmacology*, 35:851-865). Affinity-purified rabbit polyclonal or mouse monoclonal antibodies to the Kv4 channel or the PCIP protein were used for immunofluorescent detection of the target proteins.

When expressed alone, the PCIPs were diffusely distributed throughout the cytoplasm of COS-1 and CHO cells, as would be expected for cytoplasmic proteins. In contrast, when expressed alone, the Kv4.2 and Kv4.3 polypeptides were concentrated within the perinuclear ER and Golgi compartments, with some immunoreactivity concentrated in the outer margins of the cell. When the PCIPs were coexpressed with Kv4 α -subunits, the characteristic diffuse PCIP distribution changed dramatically, such that the PCIPs precisely colocalized with the Kv4 α -subunits. This redistribution of the PCIPs did not occur when they were coexpressed with the Kv1.4 α -subunit, indicating that altered PCIP localization is not a consequence of overexpression and that these PCIPs associate specifically with Kv4-family α -subunits.

To verify that the PCIP and Kv4 polypeptides are tightly associated and not simply colocalized in co-transfected cells, reciprocal immunoprecipitation analyses were performed using the PCIP and channel-specific antibodies described above. All three PCIP polypeptides coassociated with Kv4 α -subunits in cotransfected cells, as evidenced by the ability of anti-Kv4.2 and anti-Kv4.3 antibodies to immunoprecipitate the KChIP1, KChIP2, and KChIP3 proteins from lysates prepared from cotransfected cells, and by the ability of anti-PCIP antibodies to immunoprecipitate Kv4.2 and Kv4.3

α -subunits from these same lysates. The cells were lysed in buffer containing detergent and protease inhibitors, and prepared for immunoprecipitation reactions essentially as described previously (Nakahira *et al.* (1996) J. Biol. Chem., 271:7084-7089).

Immunoprecipitations were performed as described in Nakahira *et al.* (1996) J. Biol.

- 5 Chem., 271:7084-7089 and in Harlow E. and Lane, D., Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, c1988. The products resulting from the immunoprecipitation were size fractionated by SDS-PAGE and transferred to nitrocellulose filters using standard procedures.

- 10 To confirm that the cytoplasmic N-terminus of Kv4 channels is sufficient for the interaction with the PCIPs KChIP1 or KChIP2 were co-expressed with a Kv4.3 mutant (Kv4.3 Δ C) that lacks the entire 219 amino acid cytoplasmic C-terminal tail. In transiently transfected COS-1 cells, the Kv4.3 Δ C mutant was extensively trapped within the perinuclear ER and Golgi: little or no staining was observed at the outer margins of the cell. Nonetheless, KChIP1 and KChIP2 precisely colocalized with Kv4.3 Δ C in
15 cotransfected cells, and moreover, Kv4.3 Δ C was efficiently coimmunoprecipitated by PCIP antibodies, indicating that the interaction of these PCIPs with Kv4 α -subunits does not require the cytoplasmic C-terminus of the channel.

EXAMPLE 8: CO-ASSOCIATION OF PCIPs AND Kv4 CHANNELS IN NATIVE TISSUES

- 20 To determine whether PCIPs colocalize and co-associate with Kv4 subunits in native tissues, Kv4- and PCIP-specific antibodies were used for single and double-label immunohistochemical analyses and for reciprocal coimmunoprecipitation analyses of rat brain membranes. Immunohistochemical staining of rat brain sections indicated that
25 KChIP1 and KChIP2 colocalize with Kv4.2 and Kv4.3 in a region and cell type-specific manner. For example, KChIP1 colocalized with Kv4.3 in hippocampal interneurons, cerebellar granule cells, and cerebellar glomeruli, a specialized synaptic arrangement between the dendrites of cerebellar basket and golgi cells and mossy fiber terminals. KChIP2 colocalized with Kv4.3 and Kv4.2 in the dendrites of granule cells in the
30 dentate gyrus, in the apical and basal dendrites of hippocampal and neocortical

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pyramidal cells, and in several subcortical structures including the striatum and superior colliculus. Co-immunoprecipitation analyses performed using synaptic membranes prepared from whole rat brain revealed that the PCIPs (KChIPs 1, 2, and 3) are tightly associated with Kv4.2 and Kv4.3 in brain K⁺ channel complexes. Anti-PCIP antibodies immunoprecipitated Kv4.2 and Kv4.3 from brain membranes, and anti-Kv4.2 and Kv4.3 antibodies immunoprecipitated the PCIPs. None of the PCIP polypeptides were immunoprecipitated by anti-Kv2.1 antibodies, indicating that the association of these PCIPs with brain Kv channels may be specific for Kv4 α -subunits. Taken together, these anatomical and biochemical analyses indicate that these PCIPs are integral components of native Kv4 channel complexes.

EXAMPLE 9:

PCIPs ARE CALCIUM BINDING PROTEINS

To determine whether KChIPs 1, 2, and 3 bind Ca²⁺, GST-fusion proteins were generated for each PCIP and the ability of the GST-PCIP proteins, as well as the recombinant PCIP polypeptides enzymatically cleaved from GST, to bind ⁴⁵Ca²⁺ was examined using a filter overlay assay (described in, for example, Kobayashi *et al.* (1993) Biochem. Biophys. Res. Commun. 189(1):511-7). All three PCIP polypeptides, but not an unrelated GST-fusion protein, display strong ⁴⁵Ca²⁺ binding in this assay. Moreover, all three PCIP polypeptides display a Ca²⁺-dependent mobility shift on SDS-PAGE, indicating that like the other members of this family, KChIPs 1, 2 and 3 are in fact Ca²⁺-binding proteins (Kobayashi *et al.* (1993) *supra*; Buxbaum *et al.* Nef (1996). Neuron-specific calcium sensors (the NCS-1 subfamily). In: Celio MR (ed) Guidebook to the calcium-binding proteins. Oxford University Press, New York, pp94-98; Buxbaum J.D., *et al.* (1998) *Nature Med.* 4(10):1177-81.

EXAMPLE 10: ELECTROPHYSIOLOGICAL CHARACTERIZATION OF PCIPs

Because PCIPs, *e.g.*, KChIP1 (1v), KChIP2 (9ql), and KChIP3 (p19), colocalize and coassociate with Kv4 α -subunits in brain, another critical question was to determine whether these PCIPs alter the conductance properties of Kv4 channels. To address this issue, Kv4.2 and Kv4.3 were expressed alone and in combination with individual PCIPs. CHO cells were transiently-transfected with cDNA using the DOTAP lipofection method as described by the manufacturer (Boehringer Mannheim, Inc.). Transfected cells were identified by cotransfecting enhanced GFP along with the genes of interest and subsequently determining if the cells contained green GFP fluorescence. Currents in CHO cells were measured using the patch-clamp technique (Hamill *et al.* 1981. Pflugers Arch. 391: 85-100).

Transient transfection of the rat Kv4.2 α -subunit in CHO cells resulted in expression of a typical A-type K⁺ conductance. Coexpression of Kv4.2 with KChIP1 revealed several dramatic effects of KChIP1 on the channel (Figure 41 and Table 1). First, the amplitude of the Kv4.2 current increased approximately 7.5 fold in the presence of KChIP1 (amplitude of Kv4.2 alone = 0.60 +/- 0.096 nA/cell; Kv4.2 + KChIP1 = 4.5 +/- 0.55 nA/cell). When converted into current density by correcting for cell capacitance, a measure of cell surface membrane area, the Kv4.2 current density increased 12 fold with coexpression of KChIP1 (Kv4.2 alone = 25.5 +/- 3.2 pA/pF; Kv4.2 + KChIP1 = 306.9 +/- 57.9 pA/pF), indicating that KChIPs promote and/or stabilize Kv4.2 surface expression. Together with this increase in current density, a dramatic leftward shift in the threshold for activation of Kv4.2 currents was observed in cells expressing Kv4.2 and KChIP1 (activation V_{1/2} for Kv4.2 alone = 20.8 +/- 7.0mV, Kv4.2 + KChIP1 = -12.1 +/- 1.4 mV). Finally, the kinetics of Kv4.2 inactivation slowed considerably when Kv4.2 was coexpressed with KChIP1 (inactivation time constant of Kv4.2 alone = 28.2 +/- 2.6 ms; Kv4.2 + KChIP1 = 104.1 +/- 10.4 ms), while channels recovered from inactivation much more rapidly in cells expressing both Kv4.2 and KChIP1 (recovery tau = 53.6 +/- 7.6 ms) versus cells expressing Kv4.2 alone (recovery tau = 272.2 +/- 26.1 ms).

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KChIPs1, 2 and 3 have distinct N-termini but share considerable amino acid identity within the C-terminal "core" domain. Despite their distinct N-termini, the effects of KChIP2 and KChIP3 on Kv4.2 current density and kinetics were strikingly similar to those produced by KChIP1 (Table1). Thus to confirm that the conserved C-terminal core domain, which contains all three EF-hands, is sufficient to modulate Kv4 current density and kinetics, N-terminal truncation mutants of KChIP1 and KChIP2 were prepared. The KChIP1 Δ N2-31 and KChIP2 Δ N2-67 mutants truncated KChIP1 and KChIP2, respectively, to the C-terminal 185 amino acid core sequence. Coexpression of KChIP1 Δ N2-31 or KChIP2 Δ N2-67 with Kv4.2 in CHO cells produced changes in Kv4.2 current density and kinetics that were indistinguishable from the effects produced by full-length KChIP1 or KChIP2 (Table1).

To investigate whether the modulatory effects of these KChIPs are specific for Kv4 channels, KChIP1 was coexpressed with Kv1.4 and Kv2.1 in *Xenopus* oocytes. *Xenopus* oocytes were injected with 1-3 ng/oocyte of cRNA which was prepared using standard in vitro transcription techniques (Sambrook *et al.* 1989. Molecular Cloning: a laboratory manual, Cold Spring Harbor Press). Currents in oocytes were measured with a two-electrode voltage clamp. KChIP1 did not appear to have any effect on Kv1.4 or Kv2.1 currents (Table2), indicating that these functional effects may be specific for Kv4 channels. As a final control for the KChIP effects and to verify that the KChIPs' effects on Kv4 currents are independent of expression system, the above kinetic analyses were repeated after expressing Kv4.3 and KChIP mRNAs in *Xenopus* oocytes. The effects KChIP1 on for Kv4.3 in the oocyte system were strikingly similar to those on Kv4.2 in CHO cells (Table1).

Since these KChIPs bind Ca²⁺, another important question is to determine whether the effects of KChIP1 on Kv4.2 currents are Ca²⁺-dependent. This question was addressed indirectly by introducing point mutations within each of KChIP1's EF-hand domains: one mutant has point mutations in the first two EF hands (D₁₉₉ to A, G₁₀₄ to A, D₁₃₅ to A, and G₁₄₀ to A) and the other one has point mutations in all three EF hands (D₁₉₉ to A, G₁₀₄ to A, D₁₃₅ to A, G₁₄₀ to A, D₁₈₃ to A, and G₁₈₈ to A). These mutations substituted alanine for the two most highly conserved amino acids within the EF-hand consensus (Figure 25; Linse, S. and Forsen, S. (1995) Determinants that govern high-

affinity Calcium binding. In Means, S. (Ed.)Advances in second messenger and phosphoprotein research. New York, Ravens Press,. 30:89-150). Coexpression of this KChIP1 triple EF-hand mutant with Kv4.2 or Kv4.3 in COS cells indicated that this mutant colocalizes and is efficiently coimmunoprecipitated with Kv4 α -subunits in
5 COS-1 cells. However, these EF-hand point mutations completely eliminated the effects of KChIP1 on Kv4.2 kinetics (Table1). Taken together, these results indicate that the binding interaction between KChIP1 and Kv4.2 is Ca^{2+} independent, while modulation of Kv4.2 kinetics by KChIP1 is either Ca^{2+} -dependent or sensitive to structural changes induced by point mutations within the EF-hand domains.

TABLE 1

Functional effect of KchIPs on Kv4 channels

Current Parameter	rKv4.2 + vector	rKv4.2 + KchIP1	rKv4.2 + KchIP1 Δ N2-31	rKv4.2 + KchIP2	rKv4.2 + KchIP2 Δ N2-67	rKv4.2 + KchIP3	rKv4.3	rKv4.3 + KchIP1
Peak Current	0.60*	4.5*	6.0*	3.3*	5.8*	3.5*	7.7 μ A	18.1 μ A*
(nA/cell at 50 mV)	\pm 0.096	\pm 0.055	\pm 1.1	\pm 0.45	\pm 1.1	\pm 0.99	\pm 2.6	\pm 3.8
Peak Current Density	25.5	306.9*	407.2*	196.6*	202.6*	161.7*	---	---
(pA/pF at 50 mV)	\pm 3.2	\pm 57.9	\pm 104.8	\pm 26.6	\pm 27.5	\pm 21.8		
Inactivation time constant	28.2	104.1	129.2	95.1*	109.5*	67.2*	56.3	135.0
(ms, at 50 mV)	\pm 2.6	\pm 10.4	\pm 14.2	\pm 8.3	\pm 9.6	\pm 14.1	\pm 6.6	\pm 15.1
Recovery from Inactivation Time constant	272.2	53.6*	98.1*	49.5*	36.1*	126.1*	327.0	34.5*

* Significantly different from control.

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TABLE 2

Functional effects of KChIPs on other Kv channels

Current Parameter	Oocytes		Oocytes	
	hKv1.4	hKv1.4 + 1v	hKv2.1	hKv2.1 + 1v
Peak Current	8.3	6.5	3.7	2.9
(μ A/cell at 50 mV)	± 2.0	± 0.64	± 0.48	± 0.37
Inactivation time constant	53.2	58.2	1.9 s	1.7 s
(ms, at 50 mV)	± 2.8	± 6.6	± 0.079	0.078
Recovery from Inactivation time constant (sec, at -80 mV)	1.9	1.6	7.6	7.7
Activation $V_{1/2}$ (mV)	-21.0	-20.9	12.0	12.4
Steady-state Inactivation $V_{1/2}$ (mV)	-48.1	-47.5	-25.3	-23.9

**5 EXAMPLE 11: EFFECTS OF KChIP1 ON SURFACE EXPRESSION OF
KV4- α SUBUNITS IN COS-1 CELLS**

To examine the ability of KChIP1 to enhance the surface expression of Kv4 channels, the ability of KChIP1 to promote the formation of surface co-clusters of Kv4 channels and PSD-95 was monitored. PSD-95 is used to facilitate the visualization of the complex.

To facilitate the interaction between Kv4.3 and PSD-95, a chimeric Kv4.3 subunit (Kv4.3ch) was generated in which the C-terminal 10 amino acids from rKv1.4

(SNAKAVETDV, SEQ ID NO:73) were appended to the C-terminus of Kv4.3. The C-terminal 10 amino acids from rKv1.4 were used because they associate with PSD-95 and confer the ability to associate with PSD-95 to the Kv4.3 protein when fused to the Kv4.3 C-terminus. Expression of Kv4.3ch in COS-1 cells revealed that the Kv4.3ch

- 5 polypeptide was trapped in the perinuclear cytoplasm, with minimal detectable Kv4.3ch immunoreactivity at the outer margins of the cell. When Kv4.3ch was co-expressed with PSD-95, PSD-95 became trapped in the perinuclear cytoplasm and co-localized with Kv4.3ch. However, when KChIP1 was co-expressed with Kv4.3ch and PSD-95, large plaque-like surface co-clusters of Kv4.3ch, KChIP1 and PSD-95 were observed.
- 10 Triple-label immunofluorescence confirmed that these surface clusters contain all three polypeptides, and reciprocal co-immunoprecipitation analyses indicated that the three polypeptides are co-associated in these surface clusters. Control experiments indicated that KChIP1 does not interact with PSD-95 alone, and does not co-localize with Kv1.4 and PSD-95 in surface clusters. Taken together, these data indicate that KChIP1 may
- 15 promote the transit of the Kv4.3 subunits to the cell surface.

EXAMPLE 12: CHARACTERIZATION OF THE PCIP PROTEINS

In this example, the amino acid sequences of the PCIP proteins were compared to amino acid sequences of known proteins and various motifs were identified.

- 20 The 1v polypeptide, the amino acid sequence of which is shown in SEQ ID NO:3 is a novel polypeptide which includes 216 amino acid residues. Domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York), were identified by sequence alignment (see
- 25 Figure 21).

- The 8t polypeptide, the amino acid sequence of which is shown in SEQ ID NO:30 is a novel polypeptide which includes 225 amino acid residues. Calcium binding domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York), were identified by
- 30 sequence alignment (see Figure 21).

The 9q polypeptide is a novel polypeptide which includes calcium binding domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York (see Figure 21).

- 5 The p19 polypeptide is a novel polypeptide which includes calcium binding domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York (see Figure 21).

- 10 A BLASTN 2.0.7 search (Altschul *et al.* (1990) *J. Mol. Biol.* 215:403) of the nucleotide sequence of rat 1vl revealed that the rat 1vl is similar to the rat cDNA clone RMUAH89 (Accession Number AA849706). The rat 1 vl nucleic acid molecule is 98% identical to the rat cDNA clone RMUAH89 (Accession Number AA849706) over nucleotides 1063 to 1488.

- 15 A BLASTN 2.0.7 search (Altschul *et al.* (1990) *J. Mol. Biol.* 215:403) of the nucleotide sequence of human 9ql revealed that the human 9ql is similar to the human cDNA clone 1309405 (Accession Number AA757119). The human 9 ql nucleic acid molecule is 98% identical to the human cDNA clone 1309405 (Accession Number AA757119) over nucleotides 937 to 1405.

- 20 A BLASTN 2.0.7 search (Altschul *et al.* (1990) *J. Mol. Biol.* 215:403) of the nucleotide sequence of mouse P19 revealed that the mouse P19 is similar to the Mus musculus cDNA clone MNCb-7005 (Accession Number AU035979). The mouse P19 nucleic acid molecule is 98% identical to the Mus musculus cDNA clone MNCb-7005 (Accession Number AU035979) over nucleotides 1 to 583.

25 **EXAMPLE 13: EXPRESSION OF RECOMBINANT PCIP PROTEINS IN BACTERIAL CELLS**

- In this example, PCIP is expressed as a recombinant glutathione-S-transferase (GST) fusion polypeptide in *E. coli* and the fusion polypeptide is isolated and characterized. Specifically, PCIP is fused to GST and this fusion polypeptide is
30 expressed in *E. coli*, e.g., strain BI21. Expression of the GST-PCIP fusion protein in BI21 is induced with IPTG. The recombinant fusion polypeptide is purified from crude

bacterial lysates of the induced BI21 strain by affinity chromatography on glutathione beads. Using polyacrylamide gel electrophoretic analysis of the polypeptide purified from the bacterial lysates, the molecular weight of the resultant fusion polypeptide is determined.

- 5 Rat 1v and 9ql were cloned into pGEX-6p-2 (Pharmacia). The resulting recombinant fusion proteins were expressed in *E. coli* cells and purified following art known methods (described in, for example, *Current Protocols in Molecular Biology*, eds. Ausubel *et al.* John Wiley & Sons: 1992). The identities of the purified proteins were verified by western blot analysis using antibodies raised against peptide epitopes of
10 rat 1v and 9ql.

EXAMPLE 14: EXPRESSION OF RECOMBINANT PCIP PROTEINS IN COS CELLS

- To express the PCIP gene in COS cells, the pcDNA/Amp vector by Invitrogen
15 Corporation (San Diego, CA) is used. This vector contains an SV40 origin of replication, an ampicillin resistance gene, an *E. coli* replication origin, a CMV promoter followed by a polylinker region, and an SV40 intron and polyadenylation site. A DNA fragment encoding the entire PCIP protein and an HA tag (Wilson *et al.* (1984) *Cell* 37:767) or a FLAG tag fused in-frame to its 3' end of the fragment is cloned into the
20 polylinker region of the vector, thereby placing the expression of the recombinant protein under the control of the CMV promoter.

- To construct the plasmid, the PCIP DNA sequence is amplified by PCR using two primers. The 5' primer contains the restriction site of interest followed by approximately twenty nucleotides of the PCIP coding sequence starting from the
25 initiation codon; the 3' end sequence contains complementary sequences to the other restriction site of interest, a translation stop codon, the HA tag or FLAG tag and the last 20 nucleotides of the PCIP coding sequence. The PCR amplified fragment and the pcDNA/Amp vector are digested with the appropriate restriction enzymes and the vector is dephosphorylated using the CIAP enzyme (New England Biolabs, Beverly,
30 MA). Preferably the two restriction sites chosen are different so that the PCIP gene is inserted in the correct orientation. The ligation mixture is transformed into *E. coli* cells

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(strains HB101, DH5a, SURE, available from Stratagene Cloning Systems, La Jolla, CA, can be used), the transformed culture is plated on ampicillin media plates, and resistant colonies are selected. Plasmid DNA is isolated from transformants and examined by restriction analysis for the presence of the correct fragment.

- 5 COS cells are subsequently transfected with the PCIP-pcDNA/Amp plasmid DNA using the calcium phosphate or calcium chloride co-precipitation methods, DEAE-dextran-mediated transfection, lipofection, or electroporation. Other suitable methods for transfecting host cells can be found in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual*. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989. The expression of the PCIP polypeptide is detected by radiolabelling (^{35}S -methionine or ^{35}S -cysteine available from NEN, Boston, MA, can be used) and immunoprecipitation (Harlow, E. and Lane, D. *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1988) using an HA specific monoclonal antibody. Briefly, the
- 10 cells are labelled for 8 hours with ^{35}S -methionine (or ^{35}S -cysteine). The culture media are then collected and the cells are lysed using detergents (RIPA buffer, 150 mM NaCl, 1% NP-40, 0.1% SDS, 0.5% DOC, 50 mM Tris, pH 7.5). Both the cell lysate and the culture media are precipitated with an HA specific monoclonal antibody. Precipitated polypeptides are then analyzed by SDS-PAGE.
- 15 Alternatively, DNA containing the PCIP coding sequence is cloned directly into the polylinker of the pCDNA/Amp vector using the appropriate restriction sites. The resulting plasmid is transfected into COS cells in the manner described above, and the expression of the PCIP polypeptide is detected by radiolabelling and immunoprecipitation using a PCIP specific monoclonal antibody.
- 20 Rat 1v was cloned into the mammalian expression vector pRBG4. Transfections into COS cells were performed using LipofectAmine Plus (Gibco BRL) following the manufacturer's instructions. The expressed 1v protein was detected by immunocytochemistry and/or western blot analysis using antibodies raised against 1v in rabbits or mice.
- 25

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EXAMPLE 15: IDENTIFICATION AND CHARACTERIZATION OF HUMAN FULL LENGTH P19

The human full length p19 sequence was identified using RACE PCR. The sequence of p19 (also referred to as KChIP3) is shown in Figure 16. The amino acid
5 sequence of human p19 is 92% identical to the mouse p19 gene (SEQ ID NO:35).

TBLASTN searches using the protein sequence of human p19 revealed that human p19 is homologous to two sequences, Calsenilin (described in (1998) *Nature Medicine* 4: 1177-1181) and DREAM, a Ca²⁺-dependent regulator of prodynorphin and c-fos transcription (described in Carrion *et al.* (1999) *Nature* 398: 80-84). Human p19 is
10 100% identical at the nucleotide level to Calsenilin (but extends 3' to the published sequence) and 99% identical at the nucleotide level to DREAM.

The ability of p19 (as well as other PCIP family members) to co-localize with presenilin and act as transcription factors is determined using art known techniques such as northern blots, *in situ* hybridization, β -gal assays, DNA mobility assays (described in,
15 for example, Carrion *et al.* (1999) *Nature* 398:80) and DNA mobility supershift assays, using antibodies specific for KchIPs.

Other assays suitable for evaluating the association of PCIP family members with presenilins is co-immunoprecipitation (described in, for example, Buxbaum *et al.* (1998) *Nature Medicine* 4:1177).

20

EXAMPLE 16: IDENTIFICATION AND CHARACTERIZATION OF MONKEY KChIP4

In this example, the identification and characterization of the genes encoding monkey KChIP4a (jlkbd352e01t1) and alternatively spliced monkey KChIP4b
25 (jlkb231c04t1), KChIP4c (jlksa053c02), and KChIP4d (jlkx015b10) is described. TBLASTN searches in proprietary databases with the sequence of the known PCIP family members, lead to the identification of four clones jlkbb231c04t1, jlkbd352e01t1, jlksa053c02, and jlkx015b10. The four monkey clones were obtained and sequenced.

The sequences of proprietary monkey clones jlkbb231c04t1 and jlkbd352e01t1
30 were found to correspond to alternately spliced variants of an additional PCIP family member, referred to herein as KChIP4. Clone jlkbb231c04t1 contains a 822bp deletion

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relative to jlkbd352e01t1 (presumably due to splicing out of an exon), resulting in the loss of the final EF hand domain. In clone jlkbd352e01t1, the final EF hand domain is preserved, and the C-terminus is highly homologous to that of PCIP family members 1v, 9ql, and p19. Overall identity in the homologous C-termini among KChIP4, 1v, 9ql, and p19 ranged from 71%-80% at the amino acid level (alignments were performed using the CLUSTALW).

Monkey KChIP4c and KChIP4d were discovered by BLASTN search using monkey KChIP4a as a query for searching a proprietary database.

The nucleotide sequence of the monkey KChIP4a cDNA and the predicted amino acid sequence of the KChIP4a polypeptide are shown in Figure 23 and in SEQ ID NOs:48 and 49, respectively.

The nucleotide sequence of the monkey KChIP4b cDNA and the predicted amino acid sequence of the KChIP4b polypeptide are shown in Figure 24 and in SEQ ID NOs:50 and 51, respectively.

The nucleotide sequence of the monkey KChIP4c cDNA and the predicted amino acid sequence of the KChIP4c polypeptide are shown in Figure 35 and in SEQ ID NOs:69 and 70, respectively.

The nucleotide sequence of the monkey KChIP4d cDNA and the predicted amino acid sequence of the KChIP4d polypeptide are shown in Figure 36 and in SEQ ID NOs:71 and 72, respectively.

Figure 37 depicts an alignment of the protein sequences of KChIP4a, KChIP4b, KChIP4c, and KChIP4d.

Rat KChIP4 is predominantly expressed in the brain, and weakly in the kidney, but not in the heart, brain, spleen, lung, liver, skeletal muscle or testes, as indicated by northern blot experiments in which a northern blot purchased from Clontech was probed with a DNA fragment from the 3'-untranslated region of rat KChIP4.

EXAMPLE 17: IDENTIFICATION AND CHARACTERIZATION OF HUMAN AND RAT 33b07

In this example, the identification and characterization of the genes encoding rat and human 33b07 is described. Partial rat 33b07 (clone name 9o) was isolated as a

positive clone from the yeast two-hybrid screen described above, using rKv4.3N as bait. The full length rat 33b07 clone was identified by mining of proprietary databases.

The nucleotide sequence of the full length rat 33b07 cDNA and the predicted amino acid sequence of the rat 33b07 polypeptide are shown in Figure 26 and in SEQ ID NOs:52 and 53, respectively. The rat 33b07 cDNA encodes a protein having a molecular weight of approximately 44.7 kD and which is 407 amino acid residues in length.

Rat 33b07 binds rKv4.3N and rKv4.2N with slight preference for rKv4.2N in yeast 2-hybrid assays. In contrast, rat 33b07 does not bind rKv1.1N, indicating that the rat 33b07-Kv4N interaction is specific.

Rat 33b07 is expressed predominantly in the brain as determined by northern blot analysis.

The human 33b07 ortholog (clone 106d5) was also identified by mining of proprietary databases. The nucleotide sequence of the full length human 33b07 cDNA and the predicted amino acid sequence of the human 33b07 polypeptide are shown in Figure 27 and in SEQ ID NOs:54 and 55, respectively. The human 33b07 cDNA encodes a protein having a molecular weight of approximately 45.1 kD and which is 414 amino acid residues in length.

Human 33b07 is 99% identical to the human KIAA0721 protein (GenBank Accession Number: AB018264) at the amino acid level. However, GenBank Accession Number: AB018264 does not have a functional annotation. Human 33b07 is also homologous to Testes-specific (Y-encoded) proteins (TSP(Y)s), SET, and Nucleosome Assembly Proteins (NAPs). The human 33b07 is 38% identical to human SET protein (GenBank Accession Number Q01105=U51924) over amino acids 204 to 337 and 46% identical over amino acids 334 to 387.

Human SET is also called HLA-DR associated protein II (PHAPII) (Hoppe-Seyler (1994) *Biol. Chem.* 375:113-126) and in some cases is associated with acute undifferentiated leukemia (AUL) as a result of a translocation event resulting in the formation of a SET-CAN fusion gene (Von Lindern M. *et al.* (1992) *Mol. Cell. Biol.* 12:3346-3355). An alternative spliced form of SET is also called Template Activating Factor-I alpha (TAF). TAF is found to be associated with myeloid leukemogenesis

(Nagata K. *et al.* (1995) *Proc. Natl. Acad. Sci. U.S.A.* 92 (10), 4279-4283). Human SET is also a potent protein inhibitor of phosphatase 2A (Adachi Y. *et al.* (1994) *J. Biol. Chem.* 269:2258-2262). NAPs may be involved in modulating chromatin formation and contribute to regulation of cell proliferation (Simon H.U. *et al.* (1994) *Biochem. J.* 297, 389-397).

Thus, due to its homology to the above identified proteins, 33b07 may function as a protein inhibitor of phosphatase, an oncogene, and/or a chromatin modulator. The homology of 33b07 to SET, a protein phosphatase inhibitor, is of particular interest. Many channels, in particular the Kv4 channels (with which 33b07 is associated), are known to be regulated by phosphorylation by PKC and PKA ((1998) *J. Neuroscience* 18(10): 3521-3528; *Am J Physiol* 273: H1775-86 (1997)). Thus, 33b07 may modulate Kv4 activity by regulating the phosphorylation status of the potassium channel.

EXAMPLE 18: IDENTIFICATION AND CHARACTERIZATION OF RAT 1p

In this example, the identification and characterization of the gene encoding rat 1p is described. Partial rat 1p was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait.

The nucleotide sequence of the partial length rat 1p cDNA and the predicted amino acid sequence of the rat 1p polypeptide are shown in Figure 28 and in SEQ ID NOs:56 and 57, respectively. The rat 1p cDNA encodes a protein having a molecular weight of approximately 28.6 kD and which is 267 amino acid residues in length.

Rat 1p binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast two-hybrid assays. In contrast, 1p does not bind rKv1.1N, indicating that the 1p-Kv4N interaction is specific.

Rat 1p is predominantly expressed in the brain as determined by northern blot analysis.

A BLASTP 1.4 search, using a score of 100 and a word length of 3 (Altschul *et al.* (1990) *J. Mol. Biol.* 215:403) of the amino acid sequences of rat 1p revealed that rat 1p is similar to the human Restin (GenBank Accession Number P30622; also named cytoplasmic linker protein-170 alpha-2 (CLIP-170), M97501)). The rat 1p protein is

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The cytoskeleton regulates the activity of potassium channels (see, for example, Honore E, *et al.* (1992) *EMBO J.* 11:2465-2471 and Levin G, *et al.* (1996) *J. Biol. Chem.* 271:29321-29328), as well as the activity of other channels, *e.g.*, Ca^{++} channels (Johnson B.D. *et al.* (1993) *Neuron* 10:797-804); or Na^{+} channels (Fukuda J. *et al.* (1981) *Nature* 294:82-85).

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In this example, the identification and characterization of the gene encoding rat 7s is described. Partial rat 7s was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait. Rat 7s is the rat ortholog of the human vacuolar H(+)-ATPase catalytic subunit A (Accession Number P38606 and B46091) described in, for example, van Hille B. *et al.* (1993) *J. Biol. Chem.* 268 (10), 7075-7080.

The nucleotide sequence of the partial length rat 7s cDNA and the predicted amino acid sequence of the rat 7s polypeptide are shown in Figure 29 and in SEQ ID 30 NOs:58 and 59, respectively. The rat 7s cDNA encodes a protein having a molecular weight of approximately 28.6 kD and which is 270 amino acid residues in length.

Rat 7s binds rKv4.3N and rKv4.2N with preference for rKv4.3N in yeast two-hybrid assays. In contrast, 7s does not bind rKv1.1N, indicating that the 7s-Kv4N interaction is specific.

Rat 7s is expressed at significantly higher levels in the brain and the kidney than in the lung, liver, heart, testes, and skeletal muscle, as determined by northern blot analysis.

EXAMPLE 20: IDENTIFICATION AND CHARACTERIZATION OF RAT 29x AND 25r

In this example, the identification and characterization of the gene encoding rat 29x is described. Rat 29x was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait. Rat 25r is a splice variant of 29x. They differ in the 5' untranslated region, but are identical in the coding region and at the amino acid level.

The nucleotide sequence of the rat 29x cDNA and the predicted amino acid sequence of the rat 29x polypeptide are shown in Figure 30 and in SEQ ID NOs:60 and 61, respectively. The rat 29x cDNA encodes a protein having a molecular weight of approximately 40.4 kD and which is 351 amino acid residues in length.

The nucleotide sequence of the rat 25r cDNA is shown in Figure 31 and in SEQ ID NO:62. The rat 25r cDNA encodes a protein having a molecular weight of approximately 40.4 kD and which is 351 amino acid residues in length.

Rat 29x is expressed in the spleen, lung, kidney, heart, brain, testes, skeletal muscle and liver, with the highest level of expression being in the spleen and the lowest being in the liver.

Rat 29x binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast two-hybrid assays. In contrast, 29x does not bind rKv1.1N, indicating that the 29x-Kv4N interaction is specific.

Rat 29x is identical at the amino acid level to rat SOCS-1 (Suppressor Of Cytokine Signaling) described in Starr R. *et al.* (1997) *Nature* 387: 917-921; to JAB described in Endo T.A. *et al.* (1997) *Nature* 387: 921-924; and to SSI-1 (STAT-induced STAT inhibitor-1) described in Naka T. *et al.* (1997) *Nature* 387:924-928. These

proteins are characterized in that they have an SH2 domain, bind to and inhibit JAK kinase, and, as a result, regulate cytokine signaling.

As used herein, the term "SH2 domain", also referred to a Src Homology 2 domain, includes a protein domain of about 100 amino acids in length which is involved in binding of phosphotyrosine residues, *e.g.*, phosphotyrosine residues in other proteins. The target site is called an SH2-binding site. The SH2 domain has a conserved 3D structure consisting of two alpha helices and six to seven beta-strands. The core of the SH2 domain is formed by a continuous beta-meander composed of two connected beta-sheets (Kuriyan J. *et al.* (1997) *Curr. Opin. Struct. Biol.* 3:828-837). SH2 domains function as regulatory modules of intracellular signaling cascades by interacting with high affinity to phosphotyrosine-containing target peptides in a sequence-specific and strictly phosphorylation-dependent manner (Pawson T. (1995) *Nature* 373:573-580). Some proteins contain multiple SH2 domains, which increases their affinity for binding to phosphoproteins or confers the ability to bind to different phosphoproteins. Rat 29x contains an SH2 domain at amino acid residues 219-308 of SEQ ID NO:61.

Tyrosine phosphorylation regulates potassium channel activity (Prevarskaya N.B. *et al.* (1995) *J. Biol. Chem.* 270:24292-24299). JAK kinase phosphorylates proteins at tyrosines and is implicated in the regulation of channel activity (Prevarskaya N.B. *et al. supra*). Accordingly, based on its homology to SOCS-1, JAB, and SSI-1, rat 29x may modulate the activity of potassium channels, *e.g.*, Kv4, by modulating JAK kinase activity.

EXAMPLE 21: IDENTIFICATION AND CHARACTERIZATION OF RAT 5p

In this example, the identification and characterization of the gene encoding rat 5p is described. Rat 5p was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait.

The nucleotide sequence of the rat 5p cDNA and the predicted amino acid sequence of the rat 5p polypeptide are shown in Figure 32 and in SEQ ID NOs:63 and 64, respectively. The rat 5p cDNA encodes a protein having a molecular weight of approximately 11.1 kD and which is 95 amino acid residues in length.

5 Rat 5p binds rKv4.3N and rKv4.2N with similar strength in yeast two-hybrid
assays. In contrast, 5p does not bind rKv1.1N, indicating that the 5p-Kv4N interaction is
specific.

Rat 5p is expressed in the spleen, lung, skeletal muscle, heart, kidney, brain, liver, and testes, as determined by northern blot analysis.

The rat 5p is identical to rat Calpactin I light chain or P10 (Accession Number P05943). P10 binds and induces the dimerization of annexin II (p36). P10 may function as a regulator of protein phosphorylation in that the p36 monomer is the preferred target of a tyrosine-specific kinase (Masiakowski P. *et al.* (1998) *Proc. Natl. Acad. Sci. U.S.A.* 85 (4): 1277-1281).

15 Tyrosine phosphorylation regulates the activity of potassium channels
(Prevarskaya N.B. *et al. supra*). Thus, due to its identity to P10, rat 5p may modulate
the activity of potassium channels, *e.g.*, Kv4, by modulating the activity of a tyrosine-
specific kinase.

20 **EXAMPLE 22: IDENTIFICATION AND CHARACTERIZATION OF**
RAT 7g

In this example, the identification and characterization of the gene encoding rat 7q is described. Rat 7q was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait. Full length rat 7q was obtained by RACE PCR.

The nucleotide sequence of the rat 7q cDNA and the predicted amino acid sequence of the rat 7q polypeptide are shown in Figure 33 and in SEQ ID NOs:65 and 66, respectively. The rat 7q cDNA encodes a protein having a molecular weight of approximately 23.5 kD and which is 212 amino acid residues in length.

Rat 7q binds rKv4.3N and rKv4.2N with same strength in yeast two-hybrid assays. In contrast, 7q does not bind rKv1.1N, indicating that the 7q-Kv4N interaction is specific.

Rat 7q is expressed in the heart, brain, spleen, lung, liver, skeletal muscle, kidney, and testes, as determined by northern blot analysis.

Rat 7q is identical to RAB2 (rat RAS-related protein, Accession Number P05712) at the amino acid level. RAB2 appears to be involved in vesicular traffic and protein transport (Touchot N. *et al.* (1987) *Proc. Natl. Acad. Sci. U.S.A.* 84 (23): 8210-8214). Accordingly, based on its homology to RAB2, rat 7q may be involved in potassium channel, *e.g.*, Kv4, trafficking.

EXAMPLE 23: IDENTIFICATION AND CHARACTERIZATION OF RAT 19r

In this example, the identification and characterization of the gene encoding rat 19r is described. Partial rat 19r was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait. Full length rat 19r was obtained by RACE PCR.

The nucleotide sequence of the rat 19r cDNA and the predicted amino acid sequence of the rat 19r polypeptide are shown in Figure 34 and in SEQ ID NOs:67 and 68, respectively. The rat 19r cDNA encodes a protein having a molecular weight of approximately 31.9 kD and which is 271 amino acid residues in length.

Rat 19r is expressed in the heart, brain, spleen, lung, liver, skeletal muscle, kidney, and testes, as determined by northern blot analysis.

Rat 19r binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast two-hybrid assays. In contrast, 19r does not bind rKv1.1N, indicating that the 19r-Kv4N interaction is specific.

Rat 19r is identical to Rat phosphatidylinositol (PTDINS) transfer protein alpha (PTDINSTP, Accession Number M25758 or P16446) described in Dickeson S.K. *et al.* (1989) *J. Biol. Chem.* 264:16557-16564. PTDINSTP is believed to be involved in phospholipase C-beta (PLC-beta) signaling, phosphatidylinositol transfer protein (PtdIns-TP) synthesis, secretory vesicle formation, and enhancement of

phosphatidylinositol 3-kinase (PtdIns 3-kinase) activity (Cunningham E. *et al.* (1995) *Curr. Biol.* 5 (7): 775-783; (1995) *Nature* 377 (6549): 544-547; and Panaretou C. *et al.* (1997) *J. Biol. Chem.* 272 (4): 2477-2485).

- Accordingly, based on its homology with PTDINSTP, rat 19r may modulate
- 5 potassium channel, *e.g.*, Kv4, activity via the PLC-beta signaling pathway and/or the PtdIns 3-kinase signaling pathway. Rat p19r may also be involved in potassium channel, *e.g.*, Kv4, trafficking.

EXAMPLE 24: CHROMOSOMAL LOCALIZATION OF HUMAN 9q

- 10 In this example, the human PCIP 9q was chromosomally mapped using a radiation hybrid panel (Panel GB4). h9q mapped to a region of chromosome 10q that had been previously shown to contain a linkage with partial epilepsy, namely D10S192: 10q22-q24 (Ottman *et al.* (1995) *Nature Genetics* 10:56-60) (see Figure 43). Based on
- 15 proteins can serve as targets for developing anti-epilepsy drugs and as targets for medical intervention of epilepsy.

- Furthermore, h9q mapped to a region of chromosome 10q that had been previously shown to contain a linkage with IOSCA, namely D10S192 and D10S1265: 10q24- Nikali (Genomics 39:185-191 (1997)) (see Figures 42 and 43). Based on this
- 20 observation, the present invention clearly demonstrates that the 9q family of proteins can serve as targets for developing anti-spinocerebellar ataxia drugs and as targets for medical intervention of spinocerebellar ataxia.

EXAMPLE 25: KINETIC MODULATION OF KV4-CURRENT BY ARACHIDONIC ACID IS DEPENDENT ON K-CHANNEL INTERACTING PROTEINS

- 25 The voltage-gated fast-inactivating Kv4 potassium channels are thought to underlie the dendritic A-current in central neurons and the transient outward current (I_{to}) in cardiac myocytes activating at subthreshold membrane potentials. It has been
- 30 reported that arachidonic acid (AA) inhibits both the current formed by Kv4 alpha

subunits in heterologous cells and the A-current from macropatches excised from hippocampal neurons. However, actions of AA differ in that the neuronal inhibition was associated with kinetic changes that were absent *in vitro*. Most strikingly, the rate of inactivation was considerably increased upon AA application.

- 5 As indicated above, current formed by the Kv4/KChIP combination *in vitro* resembles in many aspects the A-current or I_{to} recorded *in vivo*. In this Example, the role of KChIPs in the kinetic modulation of Kv4-current by arachidonic acid is investigated using art known techniques (described in, for example, An *et al.* (2000) *Nature* 403:553-6; Keros, S. and McBain, C. J. (1997) *J. Neuroscience* 17: 3476-87; and
- 10 Villarroel, A. and Schwarz, T. L. (1996) *J. Neuroscience* 16:2522-32). In Oocytes and in CHO cells, AA inhibited peak amplitude of Kv4 independent of KChIP1. In contrast, perfusion of 10 mM of AA resulted in faster inactivation of Kv4 co-expressed with KChIP1, but did not change the rate of inactivation of Kv4 expressed alone. Thus, the AA effect on inactivation of Kv4/KChIP1 *in vitro* mimics that of the A-current in
- 15 excised neuronal patches. Taken together with the results reported above, these data support the notion that KChIPs are Kv4 auxiliary subunits and that kinetic modulation of Kv4 by AA is dependent on the presence of KChIPs.

20 **EXAMPLE 26: K-CHANNEL INTERACTING PROTEIN-2 (KChIP2) SPLICE VARIANTS, CHROMOSOMAL ORGANIZATION AND LOCALIZATION**

- In the present Example, variants of KChIP2 and their chromosomal organization were identified using standard techniques. KChIP2 genes are highly conserved at the
- 25 amino acid level among human, rat, and mouse. Multiple human splice variants were identified by database mining and cDNA library screening. Alternative splicing gives rise to N-terminal domains that are variable in length, but the core C-terminal domain is sufficient for associating with and modulating Kv4. The human KChIP2 gene spans approximately 18 kb in the q23 region of human chromosome 10 between WI-8488 and
- 30 WI-6750. This region is syntenic to mouse chromosome 19 between D19Mit40 and D19Mit11. A rat variant discovered by database mining changed the last five amino acids and maintained its ability to associate with and modulate Kv4. Therefore, these multiple variants of KChIP2 appear to function similarly in Kv4 modulation.

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Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention
5 described herein. Such equivalents are intended to be encompassed by the following claims.

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1. An isolated nucleic acid molecule selected from the group consisting of:
- 5 a) a nucleic acid molecule comprising a nucleotide sequence which is at least 60% identical to the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, or a complement thereof;
- 10 b) a nucleic acid molecule comprising a fragment of at least 583 nucleotides of a nucleic acid comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, or a complement thereof;
- 15 c) a nucleic acid molecule which encodes a polypeptide comprising an amino acid sequence at least about 60% identical to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID

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NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316;

d) a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, wherein the fragment comprises at least 15 contiguous amino acid residues of the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316; and

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e) a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, under stringent conditions.

2. The isolated nucleic acid molecule of claim 1 which is selected from the group consisting of:

a) a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, or a complement thereof; and

b) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316.

3. The nucleic acid molecule of claim 1 further comprising vector nucleic acid sequences.

4. The nucleic acid molecule of claim 1 further comprising nucleic acid sequences encoding a heterologous polypeptide.

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5. A host cell which contains the nucleic acid molecule of claim 1.
6. The host cell of claim 5 which is a mammalian host cell.
7. A non-human mammalian host cell containing the nucleic acid molecule of claim 1.
8. An isolated polypeptide selected from the group consisting of:
- a) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316;

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b) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316 under stringent conditions; and

c) a polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 60% identical to a nucleic acid comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the DNA insert of the plasmid deposited

with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316.

5 d) a polypeptide comprising an amino acid sequence which is at least 60% identical to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, 10 SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316.

15 9. The isolated polypeptide of claim 8 comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 20 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316.

10. The polypeptide of claim 8 further comprising heterologous amino acid sequences.

30 11. An antibody which selectively binds to a polypeptide of claim 8.

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12. A method for producing a polypeptide selected from the group consisting of:

- 5 a) a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316;
- 10 b) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the
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plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316; and

- c) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316 under stringent conditions;

comprising culturing the host cell of claim 5 under conditions in which the nucleic acid molecule is expressed.

13. A method for detecting the presence of a polypeptide of claim 8 in a sample comprising:

- a) contacting the sample with a compound which selectively binds to the polypeptide; and
- 5 b) determining whether the compound binds to the polypeptide in the sample to thereby detect the presence of a polypeptide of claim 8 in the sample.

14. The method of claim 13, wherein the compound which binds to the polypeptide is an antibody.

15. A kit comprising a compound which selectively binds to a polypeptide of claim 8 and instructions for use.

16. A method for detecting the presence of a nucleic acid molecule in claim 1 in a sample comprising:

- a) contacting the sample with a nucleic acid probe or primer which selectively hybridizes to the nucleic acid molecule; and
- 20 b) determining whether the nucleic acid probe or primer binds to a nucleic acid molecule in the sample to thereby detect the presence of a nucleic acid molecule of claim 1 in the sample.

17. The method of claim 16, wherein the sample comprises mRNA molecules and is contacted with a nucleic acid probe.

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18. A kit comprising a compound which selectively hybridizes to a nucleic acid molecule of claim 1 and instructions for use.

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19. A method for identifying a compound which binds to a polypeptide of claim 8 comprising:

- a) contacting the polypeptide, or a cell expressing the polypeptide with a test compound; and
- 5 b) determining whether the polypeptide binds to the test compound.

20. The method of claim 19, wherein the binding of the test compound to the polypeptide is detected by a method selected from the group consisting of:

- a) detection of binding by direct detection of test compound/polypeptide binding;
- 10 b) detection of binding using a competition binding assay; and
- c) detection of binding using an assay for PCIP activity.

21. A method for modulating the activity of a polypeptide of claim 8 comprising contacting the polypeptide or a cell expressing the polypeptide with a compound which binds to the polypeptide in a sufficient concentration to modulate the activity of the polypeptide.

22. A method for identifying a compound which modulates the activity of a polypeptide of claim 8 comprising:

- a) contacting a polypeptide of claim 8 with a test compound; and
- 20 b) determining the effect of the test compound on the activity of the polypeptide to thereby identify a compound which modulates the activity of the polypeptide.

23. A method for identifying a compound capable of treating a disorder characterized by aberrant PCIP nucleic acid expression or PCIP protein activity comprising assaying the ability of the compound or agent to modulate the expression of the PCIP nucleic acid molecule of claim 1 or the activity of the PCIP polypeptide of claim 8, thereby identifying a compound capable of treating a disorder characterized by aberrant PCIP nucleic acid expression or PCIP protein activity.

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24. The method of claim 23, wherein the disorder is a CNS disorder.
25. The method of claim 24, wherein the disorder is epilepsy.
- 5 27. The method of claim 24, wherein the disorder is spinocerebellar ataxia.
28. The method of claim 23, wherein the disorder is a cardiovascular disorder.
- 10 29. The method of claim 28, wherein the cardiovascular disorder is associated with an abnormal I_{to} current.
30. A method for determining if a subject is at risk for a disorder
- 15 characterized by aberrant or abnormal PCIP nucleic acid expression and/or PCIP protein activity comprising detecting, in a sample of cells from the subject, the presence or absence of a genetic lesion, wherein the genetic lesion is characterized by an alteration affecting the integrity of a gene encoding the PCIP polypeptide of claim 8 or misexpression of the PCIP nucleic acid molecule of claim 1.
- 20 31. The method of claim 30, wherein the disorder is a CNS disorder.
32. The method of claim 31, wherein the disorder is epilepsy.
- 25 33. The method of claim 31, wherein the disorder is spinocerebellar ataxia.
34. The method of claim 30, wherein the disorder is a cardiovascular disorder.
- 30 35. The method of claim 34, wherein the cardiovascular disorder is associated with an abnormal I_{to} current.

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36. A method for identifying a subject suffering from a disorder characterized by aberrant or abnormal PCIP nucleic acid expression and/or PCIP protein activity comprising obtaining a biological sample from the subject, and detecting in the sample, the presence or absence of a genetic lesion, wherein the genetic lesion is characterized by an alteration affecting the integrity of a gene encoding the PCIP polypeptide of claim 8 or misexpression of the PCIP nucleic acid molecule of claim 1, thereby identifying a subject suffering from a disorder characterized by aberrant or abnormal PCIP nucleic acid expression and/or PCIP protein activity.

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37. The method of claim 36, wherein the disorder is a CNS disorder.

38. The method of claim 37, wherein the disorder is epilepsy.

15 39. The method of claim 37, wherein the disorder is spinocerebellar ataxia.

40. The method of claim 36, wherein the disorder is a cardiovascular disorder.

20 41. The method of claim 40, wherein the cardiovascular disorder is associated with an abnormal I_{to} current.

42. A method for treating a subject having a potassium channel associated disorder comprising administering to the subject a PCIP polypeptide of claim 8 or portion thereof such that treatment occurs.

25

43. The method of claim 42, wherein the disorder is a CNS disorder.

44. The method of claim 43, wherein the disorder is epilepsy.

30

45. The method of claim 43, wherein the disorder is spinocerebellar ataxia.

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46. The method of claim 42, wherein the disorder is a cardiovascular disorder.

5 47. The method of claim 46, wherein the cardiovascular disorder is associated with an abnormal I_{to} current.

48. A method for treating a subject having a potassium channel associated disorder comprising administering to the subject a nucleic acid encoding a PCIP
10 polypeptide of claim 8 or portion thereof such that treatment occurs.

49. The method of claim 48, wherein the disorder is a CNS disorder.

50. The method of claim 49, wherein the disorder is epilepsy.
15

51. The method of claim 49, wherein the disorder is spinocerebellar ataxia.

52. The method of claim 48, wherein the disorder is a cardiovascular disorder.
20

53. The method of claim 52, wherein the cardiovascular disorder is associated with an abnormal I_{to} current.

54. Use of the compound identified in the method of claim 23 to treat a
25 potassium channel associated disorder.

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POTASSIUM CHANNEL INTERACTORS AND USES THEREFOR**Abstract of the Disclosure**

- The invention provides isolated nucleic acids molecules, designated PCIP
- 5 nucleic acid molecules, which encode proteins that bind potassium channels and modulate potassium channel mediated activities. The invention also provides antisense nucleic acid molecules, recombinant expression vectors containing PCIP nucleic acid molecules, host cells into which the expression vectors have been introduced, and nonhuman transgenic animals in which a PCIP gene has been introduced or disrupted.
- 10 The invention still further provides isolated PCIP proteins, fusion proteins, antigenic peptides and anti-PCIP antibodies. Diagnostic methods utilizing compositions of the invention are also provided.
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GAAATAGCCCCCTTTTCACTTCTGAGTCCCTGCATGTGCGGGGCTGAAGAAGGAAGCCAGAAAGCCTCTCTAGCGCTCGCCCTCCCA
 CGTTCTTCCTGAATACAAGACTGACAGCGAGCTCGCGGCGCTTTTCTCTCTCCATCTCAGAGTAGACAACACACAGGGGAT
 TCTTTTCTCAGGGTAGGGAGGGGCGGGGCGCGGGTCCCACCTGCATCTCAAGTCTTCCGTGCCATGGGGGCGGTCAATGG
 GCAACCTTCTCATCTCTCAAAACAAACAAAGGCGCTCGAAGATAGATTAAGATAGAGCTGGAGAGTACCATCATGGTT
 TGGCATCTGGCCCCGAGGGAGCTGGAGCAGCTCGAGGCCCAGACCAACTTCACCAAGAGGGAGCTCGAGGTCCCTTTATCTCGAGG
 TTTCCAAAAATAGGTGCCCATGTGGTGTGCTTACCCCTGCAACACCTCAGACAGATCTATCTCCTCAGTTTTCCTCTCATGGAG
 ATGTCGACAGCGTATGCCATTAACCTCTTCAATGCCCTGACACACCTCAGACAGGCTCCGTGAAGTTCGAGGACTTTTGTATA
 AACCGCTCTCTCGATTTTATGAGAGAACTCTCAGAGAAACTAAGGTGGACATTTAATTTATGTATGACACCAAGGA
 CGGATACATATAACAAAGAGGAGATATGGACATTTGTCAACGCCATCTATGACATGATGGGGAATAACACATATACCTCTGTGC
 TCAAGAGGAGCACCTCAAGGCGCATGAGCGCTCTTCCAGAAATGGACAAATAAAGATGGCATCGTAACATTTTA
 GAGACATGACCAATCAGCTCTAGAGACATTTGTAATAACCAACCTTAAACACCTGTATCTGCCCTGTGTGTAACTATTTA
 CACACCAACTCTTTGGAGACAAACACTCTTTTACATCTTTGGAAAGATTTCTCTCTGAAAGATTTCTTTATGTGAAACCCAGCAT
 CATGTGGCTCAGTCTCTGATTTGCCAACTCTTCTTCTTTCTTGAGAGAGACAGATGAAATTTGAGTTTGTGTATTCG
 GAAGACGCTACCTCTCATCTCTCATCTGCTGCTCCTATGGAAGGTCCCTCTGCTTAAGCTTTAAACAGTAGTAGTGCACAAATATTCG
 TCGTTTACGTGCCCCCAGCCCCACTGCTTCTCAAGTCAGGCGACCTTGGTGGAACTCTGGAAGCAAGAGGACCTTGAGCCAGATG
 CACACCACTCTGATGAGGCTCCCAAAACCAATGTGCTTCTCTCTTTGGTGGGAAGATGACAGTTTATCTCCAGAAACA
 ATTAGACATCTGTGATGACATGAGCATGGAGACCCCACTTAACATATATGTGGGATAGGACTGAATTTATTAAGCATATGACATT
 GTCTAGATGATCCCAACTGCGCCGG

HUMAN IV PROTEIN

MGAVMGTSLSLTKQRRFSKDKIELEWTVWCHRPGELEQLEAQTNFTKRELQVLVRGRGKNECPSGVVNEDTFKQIYAQ
YTPYPLKEDTPRQHDVDFVFORMKDKNGIGVTLDEFLDESSCOEDDNIMRSLOLFONVM

Fig. 1

RAT 1vN (r1vN) DNA (CD: 339-1037)

GGCACACAACCCCTGGATTCTTCGGAGAAATATGCCGTGAGGTGTTGCCAATTATTAGTTCTCTTGGCTAGCAGATGTTTA
 GGGACTGGTtaaGCCTTTTGAGAAATTACCTTAGGAAAAACGGGGAAATAAAAGCAAAGATTACCATGAATTGCAAGATTA
 CCTAGCAATTGCAAGGtagGAGGAGAGAGGTGGAGGGCGGAGTAGACAGGAGGGAGGGAGAAAgtgaGAGGAAGCTAGGC
 TGGTGGAATAACCCCTGCACCTTGGAACAGCGGCAAGAAGCGGATTTTCCAGCTTtaaTGCCTGCCCGCTTCTGCTT
 GCCTACCCGGGAACGGAGATGTTGACCCAGGGCGAGTCTGAAGGGCTCCAGACCTTGGGGATAGTAGTGGTCTGTGTTT
 CTCCTGAAACTACTGCACCTACCTCGGGCTGATTGACTTGTTCGGATGACAAGATCGAGGATGATCTGGAGATGACCATGG
 TTTCGCATCGGCCTGAGGACTGGAGCAGCTTGAGGCACAGACGAACCTCACCAAGAGAGAAGTGAAGTCCTTTACCGG
 GGATTCAAAAACGAGTGCCCCAGTGGTGTGGTTAACGAAAGAGACATTCAAGCAGATCTACGCTCAGTTTTTCCCTCATGG
 AGATGCCAGCACATACGCACATTACCTCTTCAATGCCTTCGACACCACCCAGACAGGCTCTGTAAAGTTCGAGGACTTTG
 TGACTGCTCTGTCGATTTTACTGAGAGGAACGGTCCATGAAAACTGAGGTGGACGTTTAAATTTGTACGACATCAATAAA
 GACGGCTACATAAACAAAGAGGAGATGATGGACATAGTGAAGCCATCTATGACATGATGGGGAAATACACCTATCCTGT
 GCTCAAGAGGACACTCCAGGCAGCACGTGGACGTCTTCTCCAGAAAAATGGATAAAAAATAAGATGGCATTGTAACTG
 TAGACGAATTTCTCGAGTCTGTGACGAGGATGACAACATCATGAGGTCTCTACAGCTGTTCAAAAATGTCATGTAACG
 AGGACACTGGCCATCCTGCTCTCAGAGACACTGACAAAACACCTCAATGCCCTGATCTGCCCTTGTTCAGTTTTACACAT
 CAACTCTCGGACAGAAATACCTTTTACACTTTGGAAGAATTCTCTGCTGAAGACTTTCTACAAAACCTGGCACCAGAGT
 GCTCAGTCTCTGATTGCCAACTCTTCCCTCCTCCTCTCTGAGAGGGACGAGCTGAAATCCGAAGTTTGTTTTGAAGC
 ATGCCCATCTCTCCATGCTGCTGCTGCCCTGTGGAAGGCCCCCTGCTTTGAGCTTAAACAGTAGTGACACAGTTTCTGCG
 TATACAGATCCCCAACTCACTGCCTCTAAGTCAGGCAGACCTGATCAATCTGAACCAATGTGCACCATCTCCGATGG
 CCTCCCAAGCAATGTGCCTGCTTCTTCTCTGGTGGGAAGAAAGAACGCTCTACAGAGCACTTAGAGCTTACCATGA
 AAATACTGGGAGAGGCAGCACCTAACACATGTAGAATAGGACTGAATTATTAAGCATGGTGGTATCAGATGATGCAACA
 GCCCATGTCATTTTTTTTTCCAGAGGTAGGGACTAATAATTCTCCACACTAGCACCTACGATCATAGAACAAGCTTTTT
 AACACATCCAGGAGGAAACCGCTGCCAGTGGTCTATCCCTTCTCTCCATCCCTGCTCAAGCCAGCACTGCATGTCT
 CTCCCGGAAGTCCAGAATGCCTGTGAAATGCTGTAACCTTTTATACCTGTTATAATCAATAACAGAACTATTTCTGTAC
 AAAAAAAAAAAAAA

RAT 1vN (r1vN) PROTEIN

MLTQGESEGLQTLGIVVVLCSLLKLLHYLGLIDLSDDKIEDDLEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNEC
PSGVVNEETFQIYAQFFPHGDASTYAHYLFNAFDTTQTGSKVFEDFVTALSILLRGTVHEKLRWTFNLYDINKDGYINK
EEMMDIVKAIYDMMGKYTYPVLKEDTPRQHVDVFFQKMDKNKDGIVTLDEFLESCQEDDNIMRSLQLFQNVN

Fig. 2 Continued

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MOUSE 1V (CD:477-1127)

CGGCCCCCTGAGATCCAGCCCCGAGCGCGGGCGGAGCGGCCGGGTGGCAGCAGGGCGGGCGGGCGGAGCGCAGCTCCCG
 CACCGCACGCGGCGCGGGCTCGGCAGCCTCGGCCGTGCGGGCACGCGGCCCCCGTGTCCAACATCAGGCAGGCTTTGGGG
 CTCGGGGCTCGGGCTCGGAGAACCAAGTGGCCCCGCTGGGTGCCCGACCGGGGGCGCCTGTCAAGGCTCCCGCGAGC
 CTCGCGCCCTGGGAGTCAGTGCATGTGCCTGGCTGAAGAAAGGCAGCAGCCAGAGCTCCAGGCGCCCCGGCCCCACGTTT
 TCTGAATACCAAGCTGCAGCGAGCTGCTCGGGCTTTTTTGCTTTCTCGCTTTTCTCTCTCCAATTCAAAGTGGGCA
 ATCCACACCGATTCTTTTTCAGGGGAGGGAAGAGACAGGGCCTGGGGTCCCAAGCAGCACACAAGTCTTCGCTGCCATGG
 GGGCCGTCATGGGCACCTTTCTCTCTCCCTGAGACCAAACAAAGGCGACCTCTAAAGACAAGATTGAGGATGAGCTAGAG
 ATGACCATGGTTTGCCACCGGCTGAGGACTGGAGCAGCTTGAGGCACAGACGAACCTTACCAAGAGAGAACTGCAAGT
 CTTGTACCGGGGATTCAAAAAAGTGCCTTAGCGGTGGTCAATGAAGAAACATTCAAGCAGATCTACGCTCAGTTTT
 TCCCTCACGGAGATGCCAGCACATATGCACATTACCCTTCAATGCCCTTCGACACCAACCAGACAGGCTCTGTAAAGTTC
 GAGGACTTTGTGACTGCTCTGTGCAATTTACTGAGAGGGACAGTCCATGAAAACTAAGGTGAGCGTTTAATTTGTATGA
 CATCAATAAAGACGCTACATAAACAAGAGGAGATGATGGACATAGTCAAAAGCATCTATGACATGATGGGGAATACA
 CCTATCTGTGCTCAAGAGGACACTCCAGGCAGCATGTGGATGTCTTCTTCCAGAAAATGGATAAAAAATAAAGATGGC
 ATTGTAACGTTAGATGAATTTCTTGAATCATGTCAGGAGGATGACAACATCATGAGATCTCTACAGCTGTTCCAAAATGT
 CATGTAACTGAGGACACTGGCCATTCTGCTCTCAGAGACACTGACAAACACCTTAATGCCCTGATCTGCCCTTGTTCCAA
 TTTTACACACCAACTCTTGGGACAGAAAATACCTTTTACACTTTGGAAGAATTCTCTGCTGAAGACTTTCTACAAAACCTG
 GCACCACGTGGCTCTGTCTCTGAGGACGAGCGGAGATCCGACTTTGTTTTGGAAGCATGCCCATCTCTTCATGCTGCTG
 CCCTGTGGAAGGCCCTCTGCTTGAGCTTAATCAATAGTGCACAGTTTTATGCTTACACATATCCCCAACTCACTGCCTC
 CAAGTCAGGCAGACTCTGATGAATCTGAGCCAAATGTGCACCATCTCCCGATGGCCTCCCAAGCAATGTGCCCTGCTTCT
 CTCTCTCTGTGGGAAGAAAGAGTGTCTACGGAACAATTAGAGCTTACCATGAAAAATTTGGGAGAGGCAGCACCTAAC
 ACATGTAGAATAGGACTGAATTATTAAGCATGGTGATATCAGATGATGCAAAATGCCCATGTCAATTTTTTCAAAGGTAG
 GGACAAATGATTCTCCACACTAGCACCTGTGGTCATAGAGCAAGTCTCTTAACATGCCAGAGGGGAACCACTGTCCA
 GTGGTCTATCCCTCTCTCCATCCCTGCTCAAAACCAGCACTGCATGCTCCCTCCAAGAGGTCAGAAATGCCTGCGAAA
 CGCTGTACTTTTTATACCTGTCTTAATCAATAAACAGAACTATTTCGTAAAAAATAAAAAAAAAA

MOUSE 1V PROTEIN

MGAVMGTFFSSLQTKQRPPSKDKIEDELEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNECPSGVVNEETFQIYIAQ
 FFFPHGDASTYAHYLFNAFDFTQTGSVKFEDFVTALSIILRGTVHEKLWTFNLYIDINKDGYINKEEMDIVKAIYDMGK
 VTYPLVKEDTPRQHVDFVFKQMDKNKDGIVTLDEFLESCQEDDNIMRSLQLFQNV

Fig. 3

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RAT 1VL DNA (CD:31-714)

GTCCCAAGTCGCACACAAGTCTTCGCTGCCATGGGGCCGTCATGGGTACCTTCTCGTCCCTGCAGACCAAAACAAAGGCG
 ACCCTCTAAAGACATCGCCTGGTGGTATTACCAAGTATCAGAGAGACAAGATCGAGGATGATCTGGAGATGACCATGGTTT
 GCCATCGGCCCTGAGGGACTGGAGCAGCTTGAGGCACAGACGAACTTCACCAAGAGAGAAGTCCAAGTCCTTTACCGGGGA
 TTCAAAAACGAGTGCCCGAGTGGTGGTTAACGAAGAGACATTCAAGCAGATCTACGCTCAGTTTTTCCCTCATGGAGA
 TGCCAGCACATACGCACATTACCTCTTCAATGCCTTCGACACCACCCAGACAGGCTCTGTAAGTTCGAGGACTTTGTGA
 CTGCTCTGTCGATTTTACTGAGAGGAACGGTCCATGAAAACTGAGGTGGACGTTTAATTTGTACGACATCAATAAGAC
 GGCTACATAAAACAAAGAGGAGATGATGGACATAGTGAAAGCCATCTATGACATGATGGGAAATACACCTATCCTGTGCT
 CAAAGGAGGACACTCCAGGCAGCAGCTGGACGCTTCTTCCAGAAAAATGGATAAAAAATAAGATGGCATGTTAAACGTTAG
 ACGAATTTCTCGAGTCCTGTCAGGAGGATGACAACATCATGAGGTCCTTACAGCTGTTCCAAAAATGTCATGTAACCTGAGG
 ACACCTGGCCATCCTGCTCTCAGAGACTGACAAAACACCTCAATGCCCTGATCTGCCCTTGTTCAGTTTACACATCAA
 CTCTCGGACAGAAATACCTTTTACACTTTGGAAGAATTCTCTGCTGAAGACTTTCTACAAAACCTGGCACCCTGGCT
 CAGTCTCTGATTGCCAACTCTTCCCTCCCTCTCTTGAGAGGAGCAGCTGAAATCCGAAGTTTGTGTTGGAAGCATG
 CCCATCTCTCCATGCTGCTGCTGCCCTGTGGAAGGCCCTCTGCTTGAGCTTAAACAGTAGTGCACAGTTTTCTGCGTAT
 ACAGATCCCCAACTCACTGCCCTCTAAGTCAGGCAGACCTGATCAATCTGAACCAAATGTGCACCATCTCCGATGGCCT
 CCCAAGCCAATGTGCTGCTTCTTCTCTGTTGGGAAGAAAGAACGCTCTACAGAGCACTTAGAGCTTACCATGAAAA
 TACTGGGAGAGGCAGCACCTAACACATGTAGAATAGGACTGAATTATTAAGCATGGTGGTATCAGATGATGCAACAGCC
 CATGTCATTTTTTTCCAGAGGTAGGACTAATAATTCTCCACACTAGCACCTACGATCATAGAACAGTCTTTTAACA
 CATCCAGGAGGAAACCGCTGCCAGTGGTCTATCCCTTCTCTCCATCCCCTGCTCAAGCCCAGCACTGCATGCTCTCTCC
 CGGAAGGTCCAGAATGCCTGTGAAATGCTGTAACTTTATACCTTGTTATAATCAATAAACAGAACTATTTCTGTAACAAA
 AAAAAAAAAAAAAA

RAT 1VL PROTEIN

MGAVMGTFSSSLQTKRRPSKDIAMWYYQYQRDKIEDDLEMTVMCHRPEGLEQLEAQTNFTKRELQVLYRGFKNECPSGVV
 NEETFQKIYAQFFPHGDASTYAHYLFNAFDTTQTGSVKFEDFVTALSILLRGTVHEKLRWTFNLNIDKNGYINKEEMMD
 IVKAIYDMMGKYTPVLKEDTPRQHVDFVQKMDKNKGIVTLDEFLESCQEDDNIMRSLLQLFQNVN

Fig. 4

MOUSE 1VL DNA (CD:77-760)

ATCCACACCGATTTCCTTTTCAGGGGAGGGAAGAGACAGGGCCTGGGGTCCCAAGACGCACACAAGTCTTCGCTGCCATGG
GGGCCGTATGGGCACCTTCTCCTCCCTGCAGACCAAAACAAAGGCACCTCTAAAGACATCGCCTGGTGGTATTACCAG
TATCAGAGAGACAAGATTGAGGATGAGCTAGAGATGACCATGGTTTGCCACCGGCCTGAGGGACTGGAGCAGCTTGAGGC
ACAGACGAACCTTACCAAGAGAGAACTGCAAGTCTTGTACCGGGATTCAAAAACAGATGCCCTAGCGGTGTGGTCAATG
AAGAAACATTCAAGCAGATCTACGCTCAGTTTTTCCCTCACGGAGATGCCAGCACATATGCACATTACCTCTTCAATGCC
TTCGACACCACCCAGACAGGCTCTGTAAAGTTCGAGGACTTTGTGACTGCTCTGTCTGATTTTACTGAGAGGGACAGTCCA
TGAAAACTAAGGTGGACGTTTAATTTGTATGACATCAATAAAGACGGCTACATAAAACAAAGAGAGATGATGGACATAG
TCAAAGCCATCTATGACATGATGGGAAAATACACCTATCCTGTGCTCAAAGAGGACACTCCCAGGCAGCATGTGGATGTC
TTCTTCCAGAAAAATGGATAAAAAATAAGATGGCATTGTAACGTTAGATGAATTTCTTGAATCATGTCCAGGAGGATGACAA
CATCATGAGATCTCTACAGCTGTTCCAAAATGTATGTAACTGAGGACACTGCCCATTCCTGCTCTCAGAGACACTGACAA
ACACCTTAATGCCCTGATCTGCCTTGTTCCAATTTTACACACCAACTCTTGGGACAGAAAAATACCTTTTACACTTTGGAA
GAATTCTCTGCTGAAGACTTTCTACAAAACCTGGCACCAGTGGCTCTGTCTCTGAGGACGAGCGGAGATCCGACTTTG
TTTTGGAAGCATGCCCATCTCTTCATGCTGCTGCCCTGTGGAAGGCCCTCTGCTTGAGCTTAATCAATAGTGACAGTT
TTATGCTTACACATATCCCAACTCACTGCCTCCAAGTCAGGCAGACTCTGATGAATCTGAGCCAAATGTGCCACCATCCT
CCGATGGCCTCCCAAGCCAATGTGCTGCTTCTCTCCTCTGGTGGGAAGAAAGAGTGTCTTACGGAACAATTAGAGCTT
ACCATGAAAAATATGGGAGAGGCAGCACCTAACACATGTAGAATAGGACTGAATATTAAGCATGGTGATATCAGATGAT
GCAAAATTGCCCATGTCTATTTTTTCAAAGGTAGGGACAAATGATTCTCCACACTAGCACCTGTGGTCATAGAGCAAGTC
TCTTAACATGCCAGAAGGGGAACCACTGTCCAGTGGTCTATCCCTCCTCTCCATCCCTGCTCAAAACCAGCACTGCAT
GTCCCTCCAAGAAGGTCCAGAATGCCTGCGAAACGCTGTACTTTTATACCTGTCTTAATCAATAAACAGAACTATTTTCG
TACAAAAA

MOUSE 1VL PROTEIN

MGAVMTGFSLSLQTKQRPSKDIWYQYQYQDKIEDELEMTVMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNEPCSGVV
NEETFQKIYAQFFPHGDASTYAHYLFNAFDTTQTGTSVKFEDFTALSILLRGTVHEKLRWTFNLYDINKDGYINKENMD
IVKAIYDMMGKYTYPVLKEDTPRQHVDFVFQKMDKNKDGIVTLDEFLESCQEDDNIIMSLQLFQNVN

Fig. 5

RAT 1VN DNA (FIRST-PASS, PARTIAL; CD: 345-955)

GTCCGGGCACACAACCCCTGGATTCTTCGAGAAATATGCCGTGACGGTGTGCCAATTATTAGTTCTCTTGGCTAGCAGA
TGTTTAGGGACTGGTTAAGCCTTTGGAGAAATACCTTAGGAAAACGGGGAATAAAGCAAAGATTACCATTGAATTGCA
AGATTACCTAGCAATTGCAAGGTAGGAGGAGAGAGGTGGAGGGCGGAGTAGACAGGAGGGAGGGAGAAAGTGAGAGGAAG
CTAGGCTGGTGGAAATAACCCCTGCACCTTGGAACAGCGGCAAGAAGCGCGATTTTCCAGCTTTAAATGCCTGCCCGCGTT
CTGCTTGCCCTACCCGGGAACGGAGATGTTGACCCAGGGCGAGTCTGAAGGGCTCCAGACCTTGGGGATAGTAGTGGTCCT
GTGTTCTCTCTGAAACTACTGCACCTACCTCGGGCTGATTGACTTGTCGGATGACAAGATCAGAGATGATCTGGAGATGA
CCATGGTTTGCCATCGGCTGAGGGACTGGAGCAGCTTGAGGCACAGACGAACCTTACCAAGAGAGAACTGCAAGTCCTT
TACCGGGGATTCAAAAACGAGTGCCCCAGTGGTGTGGTTAACGAAGAGACATTCAAGCNGATCTACGCTCAGTTTTCCTCC
TCATGGAGATGCCAGCACATACGCACATTACCTCTTCAATGCCCTTCGACACCAACCCAGACAGGCTCTGTAAAGTTCGAGG
ACTTTGTGACTGCTCTGTGCGATTTTACTGAGAGGAACGGTCCATGAAAACTGAAGTGGACGTTTAAATTTGTACGACATC
AATAAAGACGGCTACATAAAACAAAGAGGAGATGATGGACATAGTGAAAGCCATCTATGACATGATGGGGAAATACACCTA
TCTTGTGCTCAAAGAGGACACTTCCAGGCAGCACGTGGACGTCTTCTCCAGAAAATGGATAAAAAATAAAGATGG

RAT 1VN PROTEIN (PARTIAL)

MLTQGESEGLQTLGIIVVLCSSSLKLLHYLGLIDLSDDKIEDDLEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNEC
PSGVVNEETFKXIYAQFFPHGDASTAHYLFNAFDTTQTGSKVFEDFVTALSILLRGTVHEKWKTFNLYDINKDGYINK
EEMMDIVKAIYDMMGKYTYLVLEKEDTSRQHVDFVFFQKMDKNKD

Fig. 6

HUMAN 9QL DNA (CD:207-1019)

CTCACCTGCTGCCTAGTGTTCCTCTCCTGCTCCAGGACCTCCGGGTAGACCTCAGACCCCGGGCCCATTTCCAGACTCA
 GCGCTCAGCCCGGACTTCCCCAGCCCCGACAGCACAGTAGGCCGCCAGGGGGCGCCGTGTGAGCGCCCTATCCCGGCCACC
 CGGCGCCCCCTCCACGCGCCGGCGGGAGCGGGGCGCCGGGGGCCATGCGGGGCCAGGGCCGAAGGAGAGTTTGTCCG
 ATTTCCCGAGACCTGGACGGCTCCTACGACCAGCTCACGGGCCACCCCTCAGGGGCCACTAAAAAGCGCTGAAGCAGCGA
 TTCCTCAAGCTGCTGCCGTGCTGCGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAACATTAGCGCCCCAGCCTCCCTCCG
 CCCCCACAGACCCCGCTGCTGGACCCAGACAGCGTGGACGATGAATTTGAATTTGCCACCCTGTGTACCGCCTGAGG
 GTCTGGAGCAGCTGCAGGAGCAAAACAAATTCACGCGCAAGGAGTTGCAGGTCTGTACCGGGGCTTCAAGAACGAATGT
 CCCAGCGGAATTGTCAATGAGGAGAAGCTTCAAGCAGATTTACTCCCAGTTCTTTCCTCAAGGAGACTCCAGCACCTATGC
 CACTTTTCTCTTCAATGCCTTTGACACCAACCATGATGGCTCGGTCAAGTTTGGAGGACTTTGTGGCTGGTTTGTCCGTGA
 TTCTTTCGGGAACTGTAGATGACAGGCTTAATTGGGCCCTTCAACCTGTATGACCTTAACAAGGACGGCTGCATACCAAG
 GAGGAAATGCTTTGACATCATGAAGTCCATCTATGACATGATGGCAAGTACACGTACCCCTGCACTCCGGGAGGAGGCCCC
 AAGGGAACACGTGGAGAGCTTCTTCCAGAAGATGGACAGAAACAAGGATGGTGTGGTGACATTGAGGAATTCATTGAGT
 CTTGTCAAAAGGATGAGAATCATGAGGTCCATGCAGCTCTTTGACAATGTATCTAGCCCCCAGGAGAGGGGGTCAGT
 GTTCTCTGGGGGACCATGCTCTAACCCCTAGTCCAGGCGGACCTACCCCTTCTCTTCCAGGTCTATCCTCATCCTACGC
 CTCCTTGGGGGCTGGAGGGATCCAAGAGCTTGGGGATTCAAGTAGTCCAGATCTCTGGAGCTGAAGGGGCCAGAGAGTGGG
 CAGAGTGCATCTCGGGGGGTGTTCCTCAACTCCCACAGCTCTCACCCCTTCTCTGCCTGACACCCAGTGTGTAGAGTGCC
 CCTCTGTAGGAATTGAGCGGTTCCTCCACCTCCTACCTACTCTAGAAACACACTAGAGCGATGTCTCCTGCTATGTTGC
 TTCCCCATCCTTGACCTCATAAACATTTCCCTAAGACTCCCTCTCAGAGAGAATGCTCCATCTCTTGGCACTGGCTGG
 CTTCTCAGACCAGCCATTGAGAGCCCTGTGGGAGGGGGACAAGAATGTATAGGGAGAAATCTTGGGCCTGAGTCAATGGA
 TAGGTCCTAGGAGGTGGGTGGGGTTGAGAATAGAAGGGCCTGGACAGATTATGATTGCTCAGGCATACCAAGTTATAGCT
 CCAAGTTCCACAGGCTGCTACCAACAGGCCATCAAAATATAAGTTTCCAGGCTTTGCAAGAAGACTTTGTCTCCTTAGAAA
 TGCCCCAGAAATTTCCACACCTCTCTCGGTATCCATGGAGAGCTGGGGCCAGATATCTGGCTCATCTCTGGCATTTGCT
 TCCTCTCCTTCTCTCTCATGTGTGTGGTGGTGTGTGGTGGGGGAATGTGGATGGGGGATGTCCTGGCTGATGCCTGC
 CAAAATTTTCATCCACCTCTCTTGTCTTATGCTCCCTGTCTTGGAGGCTATGACTTGAGTTTGTGTTCCCATGTTCTCTA
 TAGACTTGGGACCTTCTCTGAAGTTGGGGCTATCACTCCCCACAGTGGATGCCTTAGAAGGGAGAGGGAAGGAGGAGGC
 AGGCATAGC

Fig. 7

HUMAN 9QL PROTEIN

MRGQGRKESLSDSRDLDGSYDQLTGHPGPGPTKKALKQRFLKLLPCCGPQALPSVSETLAAPASLRPHRPRLLDPDSVDDE
FELSTVCHRPEGLEQLQEQTKFTRKELQVLYRGFKNECPGIVNEENFKQIYSQFFPQGDSSTYATFLFNAFDTNHDGSV
SFEDFVAGLSVILRGTVDDRLLNNAFNLYDLNKDGCITKEMLDIMKSIYDMMGKYTYPALREEAPREHVESFFQKMDRDK
DGVVTIEEFIESCQKDNIMRSMQLFDNVI

Fig. 7 Continued

05670755.09200

RAT 9QL DNA (PARTIAL;CD:2-775)

CCGAGATCTGGACGGCTCCTATGACCAGCTTACGGGCCACCCCTCCAGGGCCCAGTAAAAAGCCCTGAAGCAGCGTTTCC
TCAAGCTGCTGCCGTCTGCGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAACATTAGCTGCCCCAGCCTCCCTCCGCCCC
CACAGACCCCGCCCGCTGGACCCAGACAGCGTAGAGGATGAGTTTGAATTATCCACGGTGTGTACCCAGCCTGAGGGCCT
GGAAACAACCTCCAGGAACAGACCAAGTTCACACGCAGAGAGCTGCAGGTCTGTACCGAGGCTTCAAGAACGAATGCCCCA
GTGGGATTGTCAACGAGGAGAATTCAAGCAGATTTATTCTCAGTTCTTTCCCCAAGGAGACTCCAGCAACTATGCTACT
TTTCTCTTCAATGCCTTTGACACCAACCACGATGGCTCTGTGAGTTTTGAGGACTTTGTGGCTGGTTTGTGCGGTATTCT
TCGGGGGACCATAGATGATAGACTGAGCTGGGCTTTCAACTTATATGACCTCAACAAGGACGGCTGTATCACAAAGGAGG
AAATGCTTGACATTATGAAGTCCATCTATGACATGATGGGCAAGTACACATACCTGCCCTCCGGAGGAGGCCCCAAGA
GAACACGTGGAGAGCTTCTTCCAGAAGATGGACAGGAACAAGGACGGCGTGGTGCATCGAGGAATTATCTCAGTCTTG
TCAACAGGACGAGAACATCATGAGGTCCATGCAGCTCTTTGATAATGTATCTAGCTCCCCAGGGAGAGGGGTTAGTGTG
TCCTAGGGTGACCAGGCTGTAGTCTTAGTCCAGACGAACTAACCTCTCTCTCCAGGCTGTCTCATCTTACCTGTAC
CCTGGGGGCTGTAGGGATTCAATATCTGGGGCTTCAGTAGTCCAGATCCCTGAGCTAAGTCACAAAAGTAGGCAAGAGT
AGGCAAGCTAAATCTGGGGGCTTCCCAACCCCGACAGCTCTACCCCTTCTCAACTGATACCTAGTCTGAGGACACCC
CTGTGTGATGGGACCAAGTGGTTCTCCACCTTCTAGTCCCACTCTAGAAAACACATTAGACAGAAGGTCTCTGCTATGGT
GCTTTCCTCATCCCTAATCTCTTAGATTTTCTCAAGACTCCCTTCTCAGAGAACACGCTCTGTCCATGTCCCCAGCTGG
GGACATGGACAGAGCGTGTCTCTAGTTCTAGATCGCGAGCGGCCGC

RAT 9QL PROTEIN (PARTIAL)

RDLDSGSDQLTGHPGPSSKALKQRFLKLLPCCGPQALPSVSETLAAPASLRPHRPLDPDSVEDEFELSTVCHRPEGL
EQLQEQTFRRELQVLIRGFKNECPSGIVNEENFKQIYSQFFPQGDSSNYATFLFNADFTNHDGSVSFEDFVAGLSVIL
RGTIDRLSWAFNLYDLNKGCIKTEMLDIMKSIYDMMGKYTPALREEAPREHVESFFQKMDRNKDGVTIIEFIESC
QQDENIMRSMQLFDNVI

Fig. 8

MOUSE 9QL DNA (CD:181-993)

CGGACTCTGAGGTGGGCCCTAAAAATCCAGCGCTCCCCAGAGAAAAGCCTTGCCAGCCCCTACTCCCGGCCCCAGCCCC
 AGCAGGTCTGCTGCGCGCCAGGGGGCACTGTGTGAGCGCCCTATCTTGGCCACCCGGCGCCCCCTCCACGGCCAGGGC
 GGAGCGGGGCGCCGGGGCCATGCGGGGCCAAGGCCGAAAGGAGAGTTTGTCCGAATCCCGAGATTGGACGGCTCCTAT
 GACCAGCTTACGGGCCACCTCCAGGGCCAGTAAAAAGCCCTGAAGCAGCGTTTCCCTCAAGCTGCTGCGCGTCTCGGG
 GCCCCAAGCCCTGCGCTCAGTCAGTGAACATTAGCTGCCCGAGCTTCCCTCCGCCCCCAGAGACCCCGCCGCTGGACC
 CAGACAGCGTGGAGGATGAGTTTGAACATCCACGGTGTGCCACCGCGCTGAGGCTCTGGAACAATCCAGGAACAAAC
 AAGTTCACACGCAGAGAGTTGCAGTCTCTGTACAGAGGCTTCAAGAACGAATGTCCAGCGGAATTGTCAACGAGGAGAA
 CTTCAAGCAAATTTATTCTCAGTCTTTTCCCAAGGAGACTCCAGCAATACGCTACTTTTCTCTTCAATGCCTTTGACA
 CCAACCATGATGGCTCTGTAGTTTGGAGACTTTGTGGCTGGTTGTGCTAGTGATCTTCGGGGAACCATAGATGATAGA
 CTGAACCTGGGCTTTCAACTTATATGACCTCAACAAGGATGGCTGTATCACGAAGGAGGAAATGCTCGACATCATGAAGTC
 CATCTATGACATGATGGCAAGTACACCTACCTGCGCTCCGGGAGGAGGCCCCGAGGGAACACGTGGAGAGCTTCTTCC
 AGAAGATGGACGAGAAACAGGACGGCGTGGTGACCATGAGGAATTCATTGAGTCTTGTCAACAGGACGAGAACATCATG
 AGGTCCATGCAACTCTTTGATAATGTCATCTAGCTCCCCAGGAGAGGGGTTAGTGTGTCCAGGGTAACCATGCTGTAG
 CCCTAGTCCAGGCAAACTTAACCTCCTCTCCCGGGTCTGTCTCATCTACCTGTACCTGGGGGCTGTAGGGGATTCA
 ACATCCTGGCGTTCAGTAGTCCAGATCCCTGAGCTAAGTGGCAGAGTAGGCAAGTAAAGTCTTTGGAGGGTGGTGGG
 GCGCGCAGATTTCCAAACCCCGACGACTCTCACCCCTTCTCGACTGATACCCAGTGTGAGGCTACCCCTGGTGTGCG
 GAACGACCAAGTGGTTCTCTGCTCCCCAGCCCACTCTAGAGACCCACACTAGACGGGAATATCTCTGCTATGGTGTCT
 TTCCCATCCTGACCGCAGATTTCTCTCTAAGACTCCCTTCTCAGAGAATATGCTTTTGTCCCTTGTCCCTGGCTGGC
 TTTTCAGCCTAGCCTTTGAGGACCTGTGGGAGGGGAGAATAAGAAAGCAGACAAATCTTGGCCCTGAGCCAGTGCTTA
 GGTCTTAGGAATCAGGCTGGAGTGGAGACAGAAAGCCTGGCGAGGCTATGAGAGCCCCAGGTTGGCTTGTCAACGCCAG
 GTTCCACAGGGCTGTGCTCTGGGTACGAGAGTATGAGTTTCCAGACTTTCCAGAAAGGCTTATGCTCTTAGCAATGTC
 CAGAAATTCACCATACACTTCTCAGTGTCTTAGGATCCAGATGTCCGGTCCATCCCTGAAACCTCTCCCTCTCTTGC
 TCTATGTTGGTGGAGTGGTGGCCAGGGGACGATGAGTGAGCCGGTGTCTGGATGATGCTGTCAAGGTCCACCTACCTT
 CCGGCTGTCAAGCCGTTCTGTTGACCTGTTTGTATCTCCATGACCCCTGTCTAGATGTAGAGGTGTGGAGTGTGCTAG
 TGGCAGCCTTAGGGGAATGGGAAGAAGCAGAGGGGCACTCCATCTGAACCCAGTGTGGGGGCATCCATTCGAATCTTTGC
 CTGGCTCCCCACAATGCCCTAGGATCCTCTAGGGTCCCCACCCCACTCTTTAGTCTACCCAGAGATGCTCCAGAGCTCA
 CCTAGAGGGCAGGGACCATAGGATCCAGGTCCAACCTGTCATCAGCATCCGGCCATGTGCTGCTGCTTATTAATAAACC
 TGCTTGTGTTTACGCGCCCTTCCCACTCAGCCAGGGTCTGAGGGGAAGGCCCCACTTTCCCGCTCTGCTCAGACATT
 GTTGACTGCTTTGACATTTGGGCTCTTCTACCTATATTTGTATATAAGAAAGACACCATCCAATAAACAACATGGC
 TATGCACAAAAA

MOUSE 9QL PROTEIN

MRGQGRKESLESRLDGSYDQLTGHPPGSKKALKQRFLLKLPCCGPQALPSVSETLAAPASLRPHRPRPLDPSVEDE
 FELSTVCHRPEGLEQLQEQTFTFRRELQVLYRGFKNECPGIVNEENFKQIYSQFFPQDSSNYATFLFNADFTNHDGVS
 SFEDFVAGLSVILRGITDRLNWFNLYDLNKDGCITKEEMLDIMKSIYDMMGKYTPALREAPREHVESFFQKMDRKN
 DGVVVTIEEFIESCQDENIMRSMQLFDNVI

Fig. 9

HUMAN 9QM DNA (CD:207-965)

CTCACCTGCTGCCTAGTGTTCCTCTCCTGCTCCAGGACCTCCGGGTAGACCTCAGACCCCGGGCCCATTTCCAGACTCA
 GCCTCAGCCCGGACTTCCCCAGCCCCGACAGCACAGTAGGCCGCCAGGGGGCCCGTGTGAGCGCCCTATCCCGGCCACC
 CGCGCCCCCTCCACGGCCCCGGCGGGAGCGGGGCCCGGGGGCCATGCGGGGCCAGGGCCCGCAAGGAGAGTTTGTCCG
 ATTTCCCGAGACCTGGACGGCTCCTACGACCAGCTCACGGGCCACCTCCAGGGCCCACTAAAAAGCGCTGAAGCAGCGA
 TTCTCTCAAGTGTCTGCCGTGCTGCGGGCCCCAAGCCCTGCCTCAGTCAGTGAAAAACAGCGTGGACGATGAATTTGAATT
 GTCCACCGTGTGTACCGGCCTGAGGGTCTGGAGCAGCTGCAGGAGCAAACAAATTACGCGCAAGGAGTTGCAGGTCC
 TGTACCGGGCTTCAAGAACGAATGTCCAGCGGAATTGTCAATGAGGAGAACTTCAAGCAGATTTACTCCCAGTTCTTT
 CCTCAAGGAGACTCCAGCACCTATGCCACTTTTCTCTCAATGCCTTTGACACCAACCATGATGGCTCGGTCAGTTTTGA
 GGACTTTGTGGCTGGTTTGTCCGTGATTCTTCGGGGAACGTAGATGACAGGCTTAATTGGGCCTTCAACCTGTATGACC
 TTAACAAGGACGGCTGCATCACAAGGAGGAAATGCTTGACATCATGAAGTCCATCTATGACATGATGGGCAAGTACACG
 TACCTTGCACTCCGGGAGGAGGCCCAAGGGAACACGTGGAGAGCTTCTTCCAGAAGATGGACAGAAACAGGATGTTGT
 GGTGACCATTGAGGAATTCATTGAGTCTTGTCAAAGGATGAGAACATCATGAGGTCCATGCAGCTCTTTGACAAATGTCA
 TCTAGCCCCCAGGAGAGGGGGTCAGTGTTTCTTGGGGGACCATGCTCTAACCCTAGTCCAGGCGGACCTCACCTTCTC
 TTCCAGGTCTATCTCATCTTACGCCTCCCTGGGGGCTGGAGGGATCCAAGAGCTTGGGGATTCAGTAGTCCAGATCTC
 TGGAGCTGAAGGGCCAGAGAGTGGGAGATGTCATCTCGGGGGTGTTCCCAACTCCACCAGCTCTCACCCCTTCCT
 GCCTGACACCCAGTGTGAGAGTGCCCCCTCTGTAGGAATTGAGCGGTTCCCACTCCTACCTTACTCTAGAAACACAC
 TAGAGCGATGTCTCTGCTATGGTGCTTCCCCCATCCCTGACCTCATAAACATTTTCCCTAAGACTCCCCCTCTCAGAGAG
 AATGCTCCATTCTTGGCACTGGCTGGCTTCTCAGACAGCCATTGAGAGCCCTGTGGGAGGGGGAAGAATGTATAGGG
 AGAAATCTTGGGCCTGAGTCAATGGATAGGTCTTAGGAGTGGGTGGGGTTGAGAATAGAAGGGCTGGACAGATTATGA
 TTGCTCAGGCATACCAGGTTATAGTCTCAAGTTCCACAGGTCTGCTACCACAGGCCATCAAATATAAGTTTCCAGGCTT
 TGCAGAAGACCTTGCTCCTTAGAAATGCCCCAGAAATTTCCACACCTCCTCGGTATCCATGGAGAGCCTGGGGCCAG
 ATATCTGGCTCATCTCTGGCATTGCTTCTCTCTTCTTCTCTGTCATGTGTGGTGGTGGTTGTGGTGGGGGAATGTGGA
 TGGGGGATGTCTGGCTGATGCCTGCCAAATTTTCATCCACCTCCTTGCTTATCGTCCCTGTTTGGAGGGCTATGACT
 TGAGTTTTTTGTTCCCATGTTCTCTATAGACTTGGGACCTTCCTGAACCTGGGGCTATCATCCTCCACAGTGGATGCCT
 TAGAAGGGAGAGGGAAGGAGGGGAGGCAGGCATAGC

Fig. 10

HUMAN 9QM PROTEIN

MRGQGRKESLSDSRDLGSDYDQLTGHPGPGPTKKALKQRFLKLLPCCGPQALPSVSENSVDDEFELSTVCHRPEGLEQLQE
QTKFTRKELQVLYRGFKNECPGIVNEENFKQIYSQFFPQGDSTYATFLFNAFDTNHDGSVSFEDFVAGLSVILRGTVD
DRLNWAFNLYDLNKDGCITKEEMLDIMKSIYDMMGKYTPALREEAPREHVESFFQKMDRNDKGVVTIEEFIESQKDEN
IMRSMQLFDNVI

Fig. 10 Continued

09670756.092700

RAT 9QM DNA (CD:214-972)

CTCACCATTGCTGCCCAAGGCTCCTGCTCTCTGCCCCAGGACTCTGAGGTGGGCCCTAAACCACGCGCTCTCTAAAGAAAAG
CCTTGCAGCCCCCTACTCCCGGCCCCCAACCCACAGAGTGCCTGCGCCGCCAGGGGGCGCTGTGTGAGCGCCCTATTCT
GGCCACC CGGCGCCCTCCACGCGCCAGGCGGGAGCGGGGCGCCGGGGCCATCGGGGCCAAGGCAGAAAAGGAGAGT
TTGTCCGAATCCCGAGATCTGGACGGCTCCTATGACCAGCTTACGGGCCACCTCCAGGGGCCAGTAAAAAAGCCCTGAA
GCAGCGTTTCTCAAGTGCTGCCGTGCTGCGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAAAACAGCTAGAGGATGAGT
TTGAATTATCACGGGTGTGTACCGACCTGAGGGCCTGGAACAACATCCAGGAACAGACCAAGTTTACACGCAGAGAGCTG
CAGGTCTGTATCCGAGGCTTCAAGAACAATGCCCAAGTGGGATTGTCAACGAGGAGAACTTCAAGCAGATTTATTCTCA
GTTCTTTCCCCAAGGAGACTCCAGCAACTATGCTACTTTTCTCTTCAATGCCTTTGACACCAACCACGATGGCTCTGTCA
GTTTTGAGGACTTTGTGGCTGGTTTGTGCTGATTCTTCGGGGGACCATAGATGATAGACTGAGCTGGGCTTTCAACTTA
TATGACCTCAACAAGGACGGCTGTATCACAAAGGAGGAAATGCTTGACATTATGAAGTCCATCTATGACATGATGGGCAA
GTACACATACCTGCCCTCCGGGAGGAGGCCCCAAGAGAACAGTGGAGAGCTTCTTCCAGAAGATGGACAGGAACAAGG
ACGGCGTGGTGACCATCGAGGAATTATCGAGTCTTGTCAACAGGACGAGAATCATGAGGTCCATGCACTCTTTTGAT
AATGTATCTAGTCTCCAGGAGAGGGGTTAGTGTGTCCTAGGGTGACCAAGCTGTAGTCTTAGTCCAGACGAACCTAA
CCCTCTCTCTCCAGGCTGTCTCATCTTACCTGTACCTGGGGGCTGTAGGGATTCAATATCCTGGGCTTTCAGTAGTC
CAGATCCCTGAGCTAAGTACACAAAAGTAGGCAAGAGTAGGCAAGCTAAATCTGGGGGCTTCCCAACCCCGACAGCTCTC
ACCCCTTCTCAACTGATACCTAGTGTGAGGACACCCCTGGTGTAGGGACCAAGTGGTTCTCCACTTCTAGTCCCACTC
TAGAAACCAACATTAGACAGAAAGTCTCCGCTATGTTGCTTTCCCATCCCTAATCTCTTAGATTTTCTCAAGACTCCC
TTCTCAGAGAACACGCTCTGTCCATGTCCCCAGCTGGCTTCTCAGCTAGCCTTTGAGGGCCCTGTGGGGAGGCGGGGAC
AAGAAAGCAGAAAAGTCTTGGCCCCGAGCCAGTGGTTAGGTCTAGGAATTGGCTGGAGTGGAGGCCAGAAAGCCTGGGC
AGATGATGAGAGCCAGCTGGGCTGTCACTGCAGGTTCCGGGGCCACAGCCCTGGGTGAGAGATGAGTTCCAGAG
CTTCCAGAAAGTCTTAGCAATGTCCAGAAATTCACCGTACACTTCTCAGTGTCTTAGGAGGGCCCGGATCCAGATG
TCTGGTTTCATCCCTGAATCCTCTCCCTCCTTCTTGCTCGTATGGTGGAGTGGTGCCAGGGGAAGATGAGTGGTGTCCC
GGATGATGCTGTCAAGGTCCACCTCCCTCCGGCTGTTCTCATGACAGTGTTTGGTCTCCATGACCCCTATCTAGA
TGTAGAGGCATGGAGTGAGTCAGGGATTTCCCGAACTTGAGTTTACCACTCTCCTAGTGGCTGCTTAGGGGAATGGG
AAGAACCCAGTGTGGGGGACCCATTAGAACTTTGCCCCGGCTCCTCAACAATGCCCTAGGGTCCCCTAGGGTACCCGCTC
CCTCTGTTTAGTCTACCCAGAGATGCTCCTGAGCTCACCTAGAGGGTAGGGACGGCTAGGCTCCAGGTCCAACCTCTCCAG
GTCAGCACCCCTGCCATGCTGCTGCTCCTATTAAACAACTGCTTGTCTCCTCCTGCGCCCCCTTCTAGTCAGCCAGGGT
CTGAGGGGAAGGGCCTCCGTTTCCCCATCCGTCAGACATGGTTGACTGCTTTTGCATTTTGGGCTCTTCTATCTATTTTG
TAAAAATAAGACATCAGATCCAATAAAACACACGGCTATGCACAAAAAAGAAAAAAGAAAAA

RAT 9QM PROTEIN

MRGQGRKESLSERDLDSYDQLTGHPGPGSKALKQRFLKLLPCCGPQALPSVSENSVEDEFELSTVCHRPEGLEQLQE
QTKFTRELQVLYRGFKNECPSGIVNEENFKQIYSQFFPQGDSSNYATFLNAPDTNHDGSVSEDFVAGLSVILRGTD
DRLSWAFNLYDLNKGDCITKEEMLDIMKSIYDMMGKYTPALREEAPREHVESFFQKMDRNKGDVVTTIEEFIESCQDEN
IMRSMQLFDNVI

Fig. 11

HUMAN 9QS DNA (CD:207-869)

CTCACCTGCTGCCTAGTGTTCCCTCTCCTGCTCCAGGACCTCCGGGTAGACCTCAGACCCCGGGCCCATCCAGACTCA
 GCCTCAGCCCGGACTTCCCCAGCCCCGACAGCACAGTAGGCCGCCAGGGGGCGCGTGTGAGCGCCCTATCCCGGCCACC
 CGGCGCCCCCTCCCACGGCCCCGGCGGGAGCGGGGCGCCGGGGCCATGCGGGCCAGGGCCCAAGGAGAGTTTGTCGG
 ATTTCCCGAGACCTGGACGGCTCCTCAGCAGCAGCTCACGGACAGCGTGGACGATGAATTTGAATTTGTCACCGTGTGTAC
 CGGCTGAGGGTCTGGAGCAGCTGCAGGAGCAAACCAATTACGCGCAAGGAGTTGACGGTCTGTACCGGGCTTCAA
 GAACGAATGTCCAGCGGAATTGTCAATGAGGAGAATTCAAGCAGATTTACTCCCAGTTCTTTCCCTAAGGAGACTCCA
 GCACCTATGCCACTTTTCTCTTCAATGCCTTTGACACCAACCATGATGGCTCGGTACGTTTTGAGGACTTTGTGGCTGGT
 TTGTCCGTGATTCTTCGGGAACTGTAGATGACAGGCTTAATTGGGCCCTTCAACCTGTATGACCTTAAACAAGGACGGCTG
 CATCACCAAGGAGGAAATGCTTGACATCATGAAGTCCATCTATGACATGATGGGCAAGTACACGTACCTGCACCTCCGGG
 AGGAGGCCCAAGGGAACACGTGGAGAGCTTCTTCCAGAAGATGGACAGAAACAAGGATGGTGTGGTGACCATTGAGGAA
 TTCATTGAGTCTTGTCAAAAGGATGAGAACATCATGAGGTCCATGCAGCTCTTTGACAATGTCTATAGCCCCCAGGAGA
 GGGGGTCAGTGTTCCTGGGGGACCATTGCTCTAACCTAGTCCAGCGGACCTCACCTTCTCTTCCCAGGTCTATCCT
 CATCTTACGCCTCCCTGGGGGCTGGAGGGATCCAAGAGCTTGGGGATTGAGTAGTCCAGATCTCTGGAGCTGAAGGGGCC
 AGAGAGTGGGCAGAGTGCATCTCGGGGGTGTTCCTCAACTCCCACCAGCTCTCACCCCTTCTTGCCTGACACCCAGTGT
 TGAGAGTGCCTTCCTGTAGGAATTGAGCGGTTCCCCACCTCCTACCTTACTCTAGAAACACACTAGAGCGATGTCTCCT
 GCTATGGTGTCTCCCCATCCTGACCTCATAAACATTTCCCTTAAGACTCCCCCTCTCAGAGAGAATGCTCCATTCTTGG
 CACTGGCTGGCTTCTCAGACCAGCCATTGAGAGCCCTGTGGGAGGGGGACAAGAATGTATAGGGAGAAATCTTGGGCTG
 AGTCAATGGATAGGTCTTAGGAGTGGGTGGGGTTGAGAATAGAAGGGCCTGGACAGATTATGATTGCTCAGGCATACCA
 GGTATATAGCTCCAAGTCCACAGGTCTGCTACCACAGGCCATCAAAATATAAGTTTCCAGGCTTTGCAAGAAGACCTTGT
 TCCTTAGAAATGCCCGAGAAATTTCCACACCTCCTCGGTATCCATGGAGAGCTGGGGCCAGATATCTGGCTCATCTC
 TGGCATTGCTTCTCTCTCTTCTTCTTCTGCATGTGTGGTGGTGGTGTGGTGGGGGAATGTGGATGGGGGATGTCTGGC
 TGATGCCGTGCAAAATTTTCATCCACCTCCTTGCTTATCGTCCCTGTTTTGAGGGCTATGACTTGAGTTTTTGTTCCTC
 ATGTTCTCTATAGACTTGGGACCTTCTGAACTTGGGGCTATCACTCCCCACAGTGGATGCCTTAGAAGGGAGAGGGAA
 GGAGGGAGGCAGGCATAGC

Fig. 12

MONKEY 9QS DNA (CD:133-795)

CCCACGCGTCCGCCACGCGTCCGCGGACGCGTGGGGTGCACTAGGCCCGCAGGGGGCGCCGTGTGAGCGCCCTATCCCG
GCCACCCGCGCGCCCCCTCCACGGAACGGCGGGGAGCGGGGCCCGCGGGGCCATCGGGGCCAGGGCCGCAAGGAGAGTT
TGTCGGAATCCCGAGACCTGGACGGAATCTACGACAGCTCACGACAGCGTGGAGGATGAATTTGAATTGTCCACCGTG
TGTCACCGGCGCTGAGGGTCTGGAGCAGCTGCAGGAGCAAACCAATTCACGCGCAAGGAGTTGCAGGTCCTGTACCGGGG
CTTCAAGAACAATGTCGAGCGGAATGTCAATGAGGAGAACTTCAAGCAAATTTATCTCCAGTTCTTTCTCCTCAAGGAG
ACTCCAGCACCTATGCCACTTTTCTCTTCAATGCCTTTGACACCAACCATGATGGCTCGGTCAAGTTTGGAGACTTTGTG
GCTGGTTTGTCGTGATCTTCTGGGGAACGTAGATGACAGGCTTAATTTGGGCTTCAACTTGATGACCTCAACAAGGA
CGGCTGCATCACAAGGAGGAATGCTTGACATCATGAAGTCCATCTATGACATGATGGGCAAGTACACATACCTGCAC
TCCGGGAGGAGGCCCCAAGGGAACATGTGGAGAACTTCTTCCAGAAGATGGACAGAAACAAGGATGGCGTGGTGACCAAT
GAGGAATTCATTGAGTCTTGTCAAAAGGATGAGAACATCATGAGGTCCATGCAGCTCTTTGACAATGTCATCTAGCCCCC
AGGAGAGGGGGTCAGTGTTCCTGGGGGACCATGCTCTAACCCTAGTCCAGGTGGACCTCACCCCTCTCTCCAGGTG
TATCCTTGTCTTAGGCTCCCTGGGGCTGGAGGGATCCAAAGCTTGGGGATTGAGTGCAGATCTCTGGAGCTGAA
GGGGCCAGAGAGTGGCAGAGTGCACTTTGGGGGTGTTCCCACTCCCAACGCTTTCACCCGCTTCTGCTGACACC
CAGTGTGAGAGTGCCCCCTCTGTAGGAACGTAGTGGTTCACCACTCTTACCCCACTCTAGAAACACACTAGACAGAT
GTCCTGTCATAGGTGCTTCCCCCATCCCTGACTTCATAAACAATTTCCCTAAAACCTCCCTTCTCAGAGAGAATGCTCCA
TTCTTGGCACTGGCTGGCTTCTCAGACCAGCCTTTGAGAGCCCTGTGGGAGGGGACAGAATGTATAGGGAGAAATCT
TGGGCTGAGTCAATGGAATAGGTCTAGGAGGTGGCTGGGGTTGAGAAATAGAAAGGCTGGACACAATGTGATTGCTCAG
GCATACCAAGTTATAGCTCCAAGTTCACAGGTCGTGACACAGGCCATCAAAATATAAGTTTCCAGGCTTTCAGAGAAG
ACCTTGCTCTCTTGGAAATGCCCCAGATATTTCCATACCCCTCTCGATATCCATGGAGAGCCTGGGGCTAGATATCTGG
CATATCCCTGGCATTTGCTTCTCTCTCTCTCTCTGCAATGTGTTGGTGGTGGTGTGGCAGGGGAATGTGGATAGGAGAT
GTCTTGGCAGATGCTTGCCTGCAAGTTCATCCCACTCCCTGCTCATCGCCCTGTTTTGAGGCTGTGACTTGAAGTTT
TGTTTCCATGTTCTCTATAGACTTGGGACCTTCTGAACTTGGGGCTATCACTCCCAAGTGGATGCTTGAAGGG
AGAGGGAAGGAGGAGGAGGAGGCAAGCAATGCAATCTGAACCCAGTGTGGGGGCACTTCACTAGGATCTTCAATCAACCCGGGCTCT
CCCCAACCCCCAGATAACCTCTCTCAGTTCCTTAGAGTCTCTCTTGTCTACTCAATCTACCAAGAGATGCCCTTAGC
ACACTCAGAGGGCAGGACCATAGGACCCAGGTTCCAACCCCATGTGTCAGCAACCCAGGCTGCTGCCATCCCTTAGCAC
ACCTGCTCGTCCCAATTCAGCTTACCTCCCACTCAGGACCAATCTGAGGGGAGGGCCCCAGAGAGCCCCCTTCCCATC
AGAAGACTGTTGACTGCTTTGCATTTTGGGCTCTCTATATATTTTGTAAAATAAGAACTATACCAAGATCTAATAAACA
CAATGGCTATGCAAAAAAAAAAAAAAAAAAAAA

MONKEY 9QS PROTEIN

MRGQGRKESLSDSRDLDSYDQLTDSVEDEFELSTVCHRPEGLEQLQEQTFRKELQVLYRGFKNECPSGIVNEENFKQ
IYSQFFPGDSSSYATFLFNAPDTHNDSVSFEDFVAGLSVILRGTVDDRNLNWFNLVDLNKDGCTKEEMLDIMKSIYD
MMGKYTPALREAPREHVENFFQKMDRNKDGVVLTIEEFIESQKDNIMRSMQLFDNVI

Fig. 13

TGTGCCCAAGGCTCTGCTCTGCCCCAGGACTCTGAGGTGGGCCCTAAAACCCAGCGCTCTCTAAAGAAAAGCCTTGC
CAGCCCCTACTCCGGCCCCCAACCCAGCAGGTGCGTGCCGCCCAGGGGGCGCTGTGTGAGCGCCCTATTCTGCCCAC
CCGGCGCCCCCTCCACGGCCACAGCGGGGAGCGGGCGCCGGGGGCCATGCGGGGCCAAGCAGAAAGGAGATTGTGTC
GAATCCCGAGATCTGGACGGCTCTCATGACCAGCTTACGGGCCACCTCCAGGGCCAGTAGAAAAGCCCTGAAGCAGCG
TTTCTCTCAAGCTGCTGCCGTGCTGCGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAAACAGCGTAGAGGATGAGTTTGAAT
TATTCACGGTGTGTGTCACCGACTGAGGGCTGGAAACAACCTCAGGAACAGACCAAGTTTACACGCAGAGAGCTGCAGGTCT
CTGTACCGAGGCTCTCAAGAACGAATGCCCCAGTGGGATTGTCAACGAGGAGAACTTCAAGCAGATTATTTCTCAGTTCTT
TCCCCAAGGAGACTCCAGCAACTATGCTACTTTTCTCTCAATGCCTTTGACACCAACACGATGGCTCTGTCAGTTTTG
AGGACTTTGTGGCTGGTTTGTGCGTGATTTCTCGGGGGACATAGATGATAGACTGAGCTGGGCTTCAACTATATAGAC
CTCAACAAAGGACGGCTGTATCAAAAGGAGGAAATGCTTGACATTATGAAGTCCATCTATGACATGATGGGCAAGTACAC
ATACCTTGCCCTCCGGGAGGAGGCCCAAGAGAACACGTGGAGAGCTTCTTCCAGAAGATGGACAGGAACAAAGCAGCGC
TGGTGACCATCGAGGAATTATCGAGTCTTGTCAACGAGGACGAGAATCATGAGGTCCATGCAGCTCTCACCCCTTCTC
AACTGATACCTAGTGCTGAGGACACCCCTGGTGTAGGGACCAAGTGGTTCTCCACCTTCTAGTCCCACCTCTAGAAAACAC
ATTAGACAGAAGGTCTCTGCTATGGTGCTTTCCCCATCCCTAATCTCTTAGATTTTCTCAAGACTCCCTTCTCAGAGA
ACACGCTCTGTCCATGTCCCAGCTGGCTTCTCAGCTTAGCCTTTGAGGGCCCTGTGGGAGGGCGGGGACAAGAAAGCAG
AAAAGTCTTGGCCCCGAGCCAGTGGTTAGTGCTTAGGAATTGGCTGGAGTGGAGGCCAGAAAGCTGGGCAGATGATGAG
AGCCCAGCTGGGCTGTCACTGCAGGTTCCGGGGCTACAGCCCTGGGTGAGCAGATGATGAGTTCCAGACTTTCCAGAA
GGTCTTTAGCAATGTCCCAGAAATTACCGGTACACTTCTCAGTGCTTTAGGAGGGCCCGGGATCCAGATGTCTGGTTCAT
CCCTGAATCTCTCCCTCTTCTTGCTCGTATGTTGGAGTGGTGGCCAGGGGAAGATGAGTGGTGTCGGGATGATGCC
TGTCAAAGGTCCCACCTCCCTCCGGCTGTTCTCATGACAGCTGTTTGGTTCTCCATGACCCCTATCTAGATGTAGAGGCA
TGGAGTGAGTCAGGGAATTTCCGGAATTTAGTGTTTTACCACCTCTCTAGTGGCTGCTCTAGGGGAATGGGAAGAACCCG
GTGCGGGCAGAGATGCTAGAACTTTTCCCGGCTCCTCAACATGCCATAGGCTCCCTAGGCTACCGCTACCCCTCTGAGTCA
TCTGACCCAGGACTGCTCTGAGCTAGCTAGGCTGAGGACGGTAGGGCTCCAGGCTCCAGCAACTCTCAGGTCAGCACCC
TGCCATGCTGCTGCTCTCATTTAACAAACCTAGCTTGGTCTCTCTCGGCCCTCTCTCAGTACGCCAGGGCTCGAGGGGAA
GGGCTCCGCTTTCCCATCCGTGAGACATGGTGTGACTGCTTTGCAATTTTGGGCTCTCTATCTATTTTGTAATAAGAA
CATCAGATCCAATAAAACACACGGCTATGCACAAAAA

MRGQGRKESLSERDLGSDYDLTGHPPGPSKKALKQRFLLKLLPCCGQALPVSSENSVEDEFELSTVCHREPGLEQLQE
QTKFTRELQVLYRGFKNECPSGIVNEENFKQIYSQFFPGQDSSNYATFLNAFDTHDGSVSFEDFVAGLSVILRGITD
DRLSWAFNLYDLNKGDCITKEEMLDIMKSIYDMGKYTPALREEAPREHVESFFQKMDRNKDGVVITIEEFIESCQQDEN
IMRSMQLSPLLN

Fig. 14

RAT 8T (9Q SPLICE VARIANT) DNA (MAY NOT BE FULL LENGTH, CD: 1-678)

ATGAACCACTGCCCTCGCAGGTGCCGGAGCCCGTTGGGGCAGGCAGCTCGATCTCTCTACCAAGTTGGTAACCTGGGTCGCT
 GTCGCCAGACAGCGTAGAGGATGAGTTTGAATTATCCACGGTGTGTACCAGACCTGAGGGCCTGGAAACAACCTCCAGGAAC
 AGACCAAGTTTACACGCAGAGAGCTGCAGGTCTGTACCAGGCTTCAAGAACGAATCCCCAGTGGGATTGTCAACGAG
 GAGAACTTCAAGCAGATTATTCTCAGTTCTTTCCCCAAGGAGACTCCAGCAACTATGCTACTTTTCTCTTCAATGCCTT
 TGACACCAACCAGATGGCTCTGTCTAGTTTGTGAGGACTTTGTGGCTGGTTTGTCTGGTGATTCTTCGGGGGACCATAGATG
 ATAGACTGAGCTGGGCTTTCAACTTATATGACCTCAACAAGGACGGCTGTATCACAAGGAGGAAATGCTTGACATTATG
 AAGTCCATCTATGACATGATGGGCAAGTACACATACCTGCCCTCCGGGAGGAGGCCCCAAGAGAACACGTGGAGAGCTT
 CTTCCAGAAGATGGACAGGAACAAGGACGGCGTGGTGACCATCGAGGAATTCATCGAGTCTTGTCAACAGGACGAGAACA
 TCATGAGGTCCATGCAGCTCTTTGATAATGTCATCTAGCTCCCCAGGAGAGGGGTAGTGTGCTCTAGGGTGACCAAGC
 TGTAGTCTTAGTCCAGACGAACCTAACCTCTCTCTCCAGGCTGTCTCTCATCTTACCTGTACCTGGGGGTGTAGGGA
 TTCAATATCTCTGGGGCTTCAGTAGTCCAGATCCCTGAGCTAAGTCACAAAAGTAGGCAAGAGTAGGCAAGCTAAATCTGG
 GGGCTTCCCAACCCCCGACAGCTCTCAACCTTCTCAACTGATACCTTAGTGTGAGGACACCCCTGGTGTAGGGACCAAG
 TGGTCTCCACCTTCTAGTCCCACTCTAGAAACCACATTAGACAGAAGGTCTCCTGCTATGTTGCTTTTCCCATCCCTAA
 TCTCTTAGATTTTCTCTAAGACTCCCTTCTCAGAGAACACGCTCTGTCCATGTCCCCAGCTGGCTTCTCAGCCTAGCCTT
 TGAGGGCCCTGTGGGGAGGCGGGGACAGAAAGCAGAAAAGTCTTGCCCCCAGAGCTAGTGGTTAGGTCTTAGGAATTGGC
 TGGAGTGGAGGCCAGAAAGCTGGGCAGATGATGAGAGCCAGCTGGGCTGTCACTGCAGGTTCCAGGGCTACAGCCCT
 GGGTCAGCAGATATGAGTTCCAGACTTTCCAGAAGTCCCTTAGCAATGTCCCAGAAATTCACCATACACTTCTCAGTG
 TCCCGGATGATGCCTGTCAAGGTCCCACTCCCTCCGGCTGTTCTCATGACAGCTGTTTGGTTCCTCATGACCCCTATC
 TAGATGTAGAGGCATGGAGTGAGTCAGGGATTTCGCCAACTTGAGTTTACCACCTCTCTAGTGGCTGCCCTAGGGGAA
 TGGGAAGAACCCAGTGTGGGGGACCCCATTAGAATCTTTGCCCGTTCCTCAAAATGCCCTAGGGTGCCCTAGGGTACCC
 GCTCCCTCTGTTTAGTCTACCCAGAGATGCTCCTGAGCTCACTAGAGGGTAGGGACGGTAGGCTCCAGGTCCAACCTCT
 CCAGGTGAGCACCCTGCCATGTCTGCTCCTCATTAACAAACCTGCTTGTCTCTCTGCGCCCCCTTCTCAGTCAGCCA
 GGGTCTGAGGGGAAGGGCTCCCGTTTCCCCATCCGTCAGACATGGTTGACTGCTTTTGCAATTTTGGGCTCTCTATCTAT
 TTTGTAATAAAGACATCAGATCCAATAAAACACACGGCTATGCACAAAAA

RAT 8T (9Q SPLICE VARIANT) PROTEIN (MAY NOT BE FULL LENGTH)

MNHCPRRCRSPLQQAARSLYLVTGSLSPDSVEDEFELSTVCHRPEGLEQLQEQTKFTRRELQVLYRGFKNECPGIVNE
 ENFKQIYSQFFPGDSSNYATFLFNADFTHDGSVSFEDFVAGLSVILRGTIDRLSWAFNLIDLNDKDCITKEEMLDIM
 KSIYDMMGKYTYPALREEAPREHVESFFQKMDRNKDGVTITIEFIESCQDENIMRSMLQFDNVI

```

>human KChIP3 cds=1-7:
ATGCAGCCGGCTAAGGAAGTGCACAAAGGCGTCGGACGGCAGCCTCCTGGGGGACCTCGGGC
ACACACCACCTTAGCAAGAA
GGAGGGTATCAAGTGGCAGAGGCCGAGGCTCAGCCGCCAGGCTTTGATGAGATGCTGCCTG
GTCAAGTGGATCCTGTCCA
GCACAGCCCCACAGGGCTCAGATAGCAGCGACAGTGAAGTGGAGCTGTCCACGGTGCGCCA
CCAGCCAGAGGGGCTGGAC
CAGCTGCAGGCCACGACCAAGTTCACCAAGAAGGAGCTGCAGTCTCTTACAGGGGCTTTA
AGAATGAGTGTCCACGGG
CCTGGTGGACGAAGACACCTTCAAACCTCATTTACGCGCAGTTCTTCCCTCAGGGAGATGCCA
CCACCTATGCACACTTCC
TCTTCAACGCCTTTGATGCGGACGGGAACGGGGCCATCCACTTTGAGGACTTTGTGGTTGGC
CTCTCCATCTCTGCTGCGG
GGCACAGTCCACGAGAAGCTCAAGTGGGCTTTAATCTCTACGACATTAACAAGGATGGCT
ACATCACCAAGAGGAGAT
GCTGGCCATCATGAAGTCCATCTATGACATGATGGGCCGCCACCTACCCCATCTGCGGG
AGGACGCGCCGGCGGAGC
ACGTGGAGAGGTTCTTCGAGAAAAATGGACCGGAACAGGATGGGGTAGTGACATTGAAGA
GTTCTCTGGAGGCTGTGACG
AAGGATGAGAACATCATGAGCTCCATGCAGCTGTTTGAAGATGTCATCTAGacacgtccaaaggagt
gcatggccacag
ccacctccacccccagaacacctccatcctgcccaggagcagcctccaaagaaacttttaaaaaatagatttgcaaaaagt
aacagattgtcacacacacacacacacacacacacacacacacacacacacacagccattcatctgggctggcagaggggac
agagttcaggaggggctgagttcgtgctaggggcgagtcagaggagcccaagccagccctcccgagggcagcgagggcag
gctgctctgggtgagtggtgacagagcaggtctgcaggccaccagctgctggatgtcaccagaaggggctcgagtg
ccctgcaggggaggggtccaatctccgggtgtgagccacactcgtcccggttctccattctgcttcttggccacacagtgggc
cgccccaggtccctggctcctcccgtagccactctctgccactacctatgctctagaagaagccctccactcag
gacccacaggggacagctggggggcaggggggagaggggtaagtggaggccaaagcctgcagctttctggaattcttcc
ctgggggtccagagatccctctgctactccactgacctggaagagctgggtaccagggccaccactgtggggcaagcctga
gtggtgaggggccaactgggcccattctccctccatggcaggaagcggggatttcaagtttagggatgggtctgtgt
gggaatctgagggcactctctgccagctccacaggggtgggtaggctctccttgcccagtcctgggtcagtgggaa
cgagtggtgggggctgtacacacccctccagcacagactgttccctccaaaggtcctcttaggtcccgagggaagcgtggt
cagagactggcagcgagggtcccggggcagagctcagagggagctctgggaaggggcggtgtccctcctctctctgtagtgc
ccctccatggcccagcagcttaggtgagccccctctcctgaagcagtgctgcgcgtccctctgcttgcacaaaaagcac
aagcatctctagcagctcaggggcagccctagtgggagccagcacactgctctcggaggccagggccctcctgctggc
tgaggtctggggccagctagccccaatatggtggccctggggaagagccttgggggctgtgctctgctgctggatcagtg
gggccccaaagcccgccgggtgaccacaattcaaaagcacaaacctggggactgtgcttggtgtccctccatctg
ggatggagaatgccagcccaagctggagccaatggtgagggctgagagggctgtggtgggtggtcagcagaaaacccc
caggagggagagatgctgctcccgctgattggggctcaccacagaaggaacccggtccagggcgcatggccctcca
ggaaacattccacataatattccatcacagccagccagctccactcagggttgggccggggaggtccccgtgtgoccc
aagaggtcagcccggtgagcaggggcccctcagagggaagggcagtagtgggagggccatgggggccccctcgccattac
acacagcctggcctccctgaggagctgcatggagcctggctccaggtccaggtgactgggggctctgctccaggg
agggcatcagctttccctggctcaggagatcttctccctccctcaccgcgtgccagccctccagctgggtgtaactctg
cctcaaggccaagcctcaggagagcatcaccaccacaccctcgccgcttggtctggggccagagctgggtgcacag
cccaaccaggaggggtgctgctcccagctgggacacagggcccgctgctgcatggcagaagcgtctccagggcc
acggcctgggaggggtggttctctgctcagcatccactaatattcagtcctgtatattttaaaaaaacttgacaaa
ggaaaaaataaataaattctcgccgcgcttccca

```

Fig. 16

>human KChIP3
MQPAKEVTKASDGSLLGDLGHTPLSKKEGIKWQRPRLSRQALMRCCLVKWILSSTAPQGSDDSD
SELELSTVRHQPEGLD
QLQAQTKFTKKELQSLYRGFKNECPTGLVDEDTFKLIYAQFFPQGDATTYAHFLFNAFDADGNG
AIHFEDFVVGLSILLR
GTVHEKCLKWAFNLYDINKDGYITKEEMLAIMKSIYDMMGRHTYPILREDAPAEHVERFFFEKMD
RNQDGVVTIEEFLEACQ
KDENIMSSMQLFENVI

Fig.16 Continued

RAT P19 DNA (FIRST PASS, PARTIAL; CD:1-330)

TTTGAGGACTTTGTGGTTGGGCTCTCCATCCTGCTTCGAGGGACCGTCCATGAGAAGCTCAAGTGGGCCTTCAATCTCTA
CGACATCAACAAGGACGGTTACATCACCAAAGAGGAGATGCTGGCCATCATGAAGTCCATCTACGACATGATGGGCCGCC
ACACCTACCCTATCCTGCGGGAGGACGCACCTCTGGAGCATGTGGAGAGGTTCTTCCAGAAAATGGACAGGAACCAGGAT
GGAGTAGTGACTATTGATGAATTTCTGGAGACTTGTGAGAAGGACGAGAACATCATGAGCTCCATGCAGCTGTTTGAGAA
CGTCATCTAGGACATGTAGGAGGGGACCTGGGTGGCCATGGGTTCCTCAACCCAGAGAAGCCTCAATCCTGACAGGAGAA
GCCTCTATGAGAAACATTTTTCTAATATATTTGCAAAAAGTG

RAT P19 PROTEIN (PARTIAL)

FEDFVVGLSILLRGTVHEKWKWAFNLYDINKDGYITKEEMLAIMKSIYDMMGRHTYPILREDAPLEHVERFFQKMDRNQD
GVVTIDEFLETCKDENIMSSMLFENVI

Fig.17

MOUSE P19 DNA (CD: 49-819)

CGGGCTGCAAAGCGGAAGSTTAGTGACGGTCCCTTTTCAGCAGCAGAGATGCAGAGGACCAAGGAAGCCGTGAAGGCATC
 AGATGGCAACCTCCTGGGAGATCCTGGGGCGCATACCACTGAGCAAGAGGGAAGCATCAAGTGGCAAGGCCACCGGTTCA
 CCCGCCAGGCCCTGATGCGTGTGCTGCTTAATCAAGTGGATCCTGTCCAGTGTGCCCAACAAGGCTCAGACAGCAGTGAC
 AGTGAACGTGGAGTTATCCACGGTGCGCCATCAGCCAGAGGGCTTGGACCAGCTACAAGCTCAGACCAAGTTACCAAGAA
 GGAGCTGCAGTCCCTTTACCGAGGCTTCAAGAATGAGTGTCCACAGGCTGGTGGATGAAGACACCTTCAAACCTCATTT
 ATTCCAGTTCTTCCCTCAGGAGATGCCACCACCTATGCACACTTCTCTTCAATGCCTTTGATGCTGATGGGAACGGG
 GCCATCCACTTTGAGGACTTTGTGTTGGGCTCTCCATCCTGCTTCGAGGGACGGTCCATGAGAAGCTCAAGTGGGCCCTT
 CAATCTCTATGACATTAACAAGGATGGTGCATCAACCAAGGAGAGATGCTGGCCATCATGAAGTCCATCTACGACATGA
 TGGGCCGCCACACTACCCCATCCTGCGGGAGGATGCACCCCTGGAGCATGTGGAGAGGTTCTTTCAGAAAATGGACAGG
 AACCAGGATGGAGTGGTACCATTGATGTATTCTTGGAGACTTGTCAAGAGGATGAGAATCATGAACCTCCATGCAGCT
 GTTTGAGAAGCTCATCTAGGACATGTGGGAGGGGACCCAGTGGTCAATTGCTTCTCAACCCAGAGSAGCCTCAATCTCTGA
 CAGGAGAAGCCTCTATGAGAAACATTTTCTAATATATTGCAAAAAGTGAGCAGTTTACTTCCAAGACACAGCCACCGT
 CACACACAGACACAGACATACAGACACACACACACACACATGGTCTCTGCTTGGCCAGGAAAGTGGCAGCC
 AGAAGGCCCCCCGCTTATCTTAGGTCAATAAAAAGGCTGCTCTCTGGGATGGCCAGCCCTGGCTAGATGTTACCCACA
 AGGAACCTCAGAGATCGAGAGGACCAGGTCTACAAAGCTAAGGTCCCTGTGTCTTTTCTACCACTCGGGAGATCAAACCTAC
 TCCTGCCTATGACCCATGCTCTTAGGAAGCTCCCAGAAATCCAAGGGGACAAAGAGGGGAGAGGTTCTATAGGAAGAA
 ATGGTTTGGGAAGCTGGGCTTGACGCCCTTATGCTAATGATCACCTGGGGTCTTGGAACCCGAGTGCCAGGCTACCTACTA
 TGCCGTGAGCTTAGATAGTGAGGGGCCATTGGACTAAGACCTCCTGTAAGAGTGGGGCAGGATTGAGGTTTGTGGAGAAA
 CTGAGGAAACAATTTGTCCATACCCTGGGTGAAGACTGCTGGCCAGTGGGAATGTGGCTGGTGGAGATTTCCCAACTTC
 CAGCACCAGGATGGCTCTCCAAGGTCTCTTTGATTCCCTGGGGAGATCACTGGCTCATAGACTGCAACACAGGGAAC
 TGGGCTGAAAATGGGAGGTCTGGTAGGGGCCATCCCCCTCTTTTCCCTGGCCAATTGCCACCCAGTTCTCTTAACACAGTG
 GATCGGCCACACCTCTGTGGCTGCCCTTGAACAGACTCATCCCGACCAAGACAAAAAGCACTAACTCCTAGCAGCTCAG
 GCCAAGCCCAACAGGGAAGGCTGGGTCCCTGCAGCCCTGATTAGTGGCCAGGAAGACGCTCAGACATCCATCCTGTA
 CCTCGGAGCCTTGGGGTCTCAGAGCCCTTTCCAGCCAGCTCGCCAACATTTCAAAGCAAAACCTGCGGATTCTGCT
 TGCTTGGGCTGCGCCCTGGGATTGAAGGCCACTGTTAACCTAAGCTGGAGCTAGCCCTGAGGGCTGGGGACCTGTGAC
 CAGGCAACAGGTGACAGACCCCTCAGGAGGAGAGAGCTGTCTCTGCCCTCCCGAGGCTCGCCAGAAAGAACAGTGTG
 CCAAGAAGCATGTTTCTGGAGGAACATCCCCACAAAAGTACATTCCATCATCTGAAGCCCGGCTCTGTGCTCAGGCTG
 CTCTGAAAGTCCACGTGTGTCTCCAGAGGCCAGCCCCAAGATAAGGGAGGTCTTGAAGGAAGGACAGGGTGACAAACA
 CCCCTATACACAGGTGGACCCCCCTCTGAGGACTGTACTGACCCCATCTCCATCCTGACCGGGGCTTCCCTTTACCCGA
 TCTACAGACCACAGTTCTCCCTGGCTCAGGGACCCCTGTCCCCAGTCTGACTCTTCCCATCGAGGTCCCTGTCTTGT
 GAAAAGCCAAGGCCACGGGAAAAGGCCACCACCTCTAACCTGTGCTATCCCTTAGCCTCTGGCTGCACGCCAACCTGGAG
 GGGTCTGTCCCTTTTCAGGAGACACAGACTGGCCGCATGTCCGATGGCAGAAGCGCTCTCCCTTGGGTGCAGCCTGGAAG
 GGTGGTTCTGTCTCAGCGCCACCAATATTTCAGTCCATATATATTTTAAATAAAGAAACTTGACAAAGGAAAAAATAA
 AAAA

Fig. 18

>AI 352454 (partial) cds = 1-339

CACGAGGTGGAAAGCATTTTCGGCTCAGCTGGAGGAGGCCAGCTCTACAGGCGGTTTCCTGT
 ACGCTCAGAACAGCACCAA
 GCGCAGCATTAAAGAGCGGCTCATGAAGCTCTTGCCCTGCTCAGCTGCCAAAACGTCGTCTC
 CTGCTATTCAAAACACGG
 TGGAAAGATGAACCTGGAGATGGCCACCGTCAGGCATCGGCCCGAAGCCCTTGAGCTTCTGGA
 AGCCCAGAGCAAATTTACC
 AAGAAAGAGCTTCAGATCCTTTACAGAGGATTTAAGAACGTAAGAAGCTTCTTTTGAATTT
 ACCTTCACACAATTCCCA
 GAGGAGCATTGAGAAATGAgagggaaaagggggaaaatatccattctatgagaagccccatcatatgtatatttcatact
 gatccttcccagataggaatataatcagtatctgtggactttgaatctctgtggcacacccatgctggcatactgtaatt
 gcccattaacaaanagtttttgagaaaaaaaaaaaaaaaaaaaaaaaaaaaaa

>AI352454

HEVESISAQLEEASSTGGFLYAQNSTKRSIKERLMKLLPCSAAKTSSPAIQNSVEDELEMATVRHR
 PEALELLEAQSKFT
 KKELQILYRGFKNVRTFFLTLP SHNSQRSIEK

Fig. 19

P193 (AA349365) DNA (CD:2-127,patial)

TGAAGGTTCTTCGAGAAAATGGACCGGAACAGGATGGGGTAGTGACCATTTGAAGAGTTCTCGGAGG
 CTGTGAGAGGATGAGAACATCATGAGCTCCATGCAGCTGTTTGAGAATGTCACTAGGACACGTCCTCAAA
 GGAGTGCATGGCCACAGGCCACCTCCACCCCCAAGAAAACCTCCATCTGCCAGGAGCAGCCTCCAAGAAA
 CTTTTAAAAATAGATTTCGAAAAAGTGAACAGATTGTCTACACACACACACACACACACACACAC
 ACACACACACAGCCATTCACTCGGGCTGGCAGAGGGGACAGAGTTTCAGGAGGGGGCTGAGTCTGGCTAG
 GGGCCGAGTCCAGGAGCCCCAGCCAGCCCTTCCAGGCCAGCGAGGCGAGGCTGCCTCTGGGTGAGTGG
 CTGACAGAGCAGGCTGTCAGGGCCACCAGCTGCTGGATGTCACCAAGAAAGGGGCTCGAGTGCCTTGCAG
 GGGAGGGTCCAATCTCCGGTGTGAGGCCACCTCGTCCGTTCTCCATTCTGCTTTCTTGCCACACAGTGGG
 CCGGCCCCAGGCTCCCCCTGGTCTCCTCCCGTAGCCACTCTCTGCCCACTACCTATGCTTCTAGAAAGCCC
 CTCACCTCAGGACCCAGAGGGACAGCTGGGGGGCAGGGGGGAGAGGGGGTAATGGAGGCCAAGCCT
 GCAGCTTTCTGAAAATTCTTCCTTGGGGGTCCAGGATCCCCCTGCTACTCCACTNACCTGGAAGAGCTGG
 GTACCAAGGCCACCCACTGTGGGGCAAGCCTGAGTGGTGAGGGGCCACTGGGCCCCATTCTCCCTCCATGG
 CAGGAAGCGGGGGATTTCAGTTTAGGGATTGGGTCTGGTGGAGAATCTGAGGGCACTCTCTGCCAG
 CTCACAGGGTGGGATGAGCCTCTCCTTGCCCCAGTCTCGTTTCACTGAGGAATGCAGTGGGTGGGGCIGT
 ACACACCTTCCAGCACAGACTGTTCCCTCCAAGGTCCTCTTAGGTCCCGGAGGAACGTGGTTTCAGAGAC
 TGGCAGC CAGGGAGGCCGGGGCAGAGCTCAGAGGAGTCTGGGAAGGGGCGTGTCCCTCTTCTCTGTGA
 GTGCCCTTCCATGGCC CAGCAGCTTGGCTGAGCCCCCTCTCTTGAAGCAGTGTGCGCGTCCCTCTGCTCT
 GCACAAAAGCACAAAGCATTCCTTAGCAGCTCAGGCGCAGCCCTAGTGGGAGCC CAGCACACTGCTTCT
 CGGAGGCC CAGGCCCTCTGCTGGCTGAGGCTTGGGCCCCAGTAGCCCCAATATGGTGGCCCTGGGGGAAGA
 GGCTTGGGGGTCTGCTCTGTGCTGGGATCAGTGGGGCCCCAAAGCC CAGCCGGCTGACCAACATTCA
 AAAGCACAACCCCTGGGGACTCTGCTTGGCTGTCCCTCCATCTGGGGATGGAGAATGCCAGGCCAAAG
 CTGGAGCCAAATGGTGAGGGCTGAGAGGGCTGTGGCTGGGTGGTCAGCAGAAACCCCCAGGAGGAGAGA
 GATGCTGTCTCCCGCTGATTGGGGCTCACCAGAAAGGAACCCGGTCCCAGGCCGATGGCCCCCTCCAGG
 AACTTCCCATATAATACATTCCATCACAGCCAGCCCCAGCTCCACTCAGGGCTGGCCCGGGGAGTCCCCG
 TGTGCCCAAGAGGCTAGCCCCAGGGTGAAGAGGGCCCTCAGAGGAAAGGCAGTATGGCGGAGGCCATG
 GGGGCCCTCTGGCATTCACACACAGCCTGGCCCTCCCTGCGGAGCTGCATGGACGCCCTGGCTCCAGGCTC
 CAGGCTGACTGGGGGCTCTGCTCCAGGAGGGCAGTCAAGCTTTCCCTGGCTCAGGGAATCTTCTCCCTCCC
 CTCACCCGCTGCCAGCCCTCCAGCTGGTGTCACTCTGCCTCTAAGGCC CAGGGCTCAGGAGAGCATCA
 CCACACACCCCTGCCGGCTTGGCCTTGGGGCCAGACTGGCTGCACAGCCCAACAGGAGGGGTCTGC
 CTCCACCGTGGGACACAGACGGCCGATGTCTGCATGGCAGAGCGTCTCCCTTGGCCACGGCTGGG
 AGGGTGGTTCTGTCTTCAGCATCCACTAATATTCTAGTCCGTATATTTTAATAAAATAAACTTGACAAA
 GAAAAAAAAAAAAAAAAA

P193 PROTEIN (PARTIAL)

ERFFEKMDNRQDGVVTTIEEFLEACQKDENIMSSMQLFENVII

Fig. 20

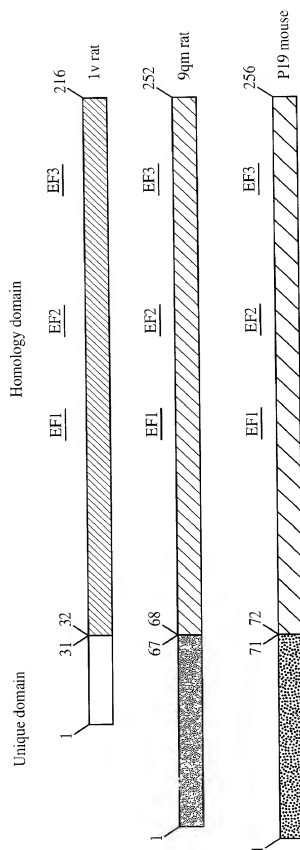


Fig. 21

A. exon1 sequence (with introns included):

CGGGAGGAGAGAGAGGCAGCTTCGGCTCGGCTCCGGCTCAGCTCCGCTTCGCCCTCCGGCTTCGCGCTACCTTCGCTGCCAT
AGTGTTCCTCCCTCTCTGCTCCAGGACCTCCGGGTAGACCTCAGACCCCGGGGCCATATCCCAGACCTACGCCCTCAGCCGCC
CATCTCCCCACCTCCGCCAGACAGTAAAGCCGACAGGGGGCCGCTGTAGCGCCCATATCCGGCCACCCGGCGCCG
CCCTCCACCGCCCGGGCGGGCGAGCGGGGCGCGGGGGCCATTCGGGGCAGGGCCGGAAGAGAGTTTGTCCGATATCC
CGAGACTCTGGACGGCTCTTACGACCACTACAGGCTAGTCAGTAGTGGGGGTTCGGGGAGGGAGGGGTGGATTCC
ATTCTCTCAGACACTCTCCGCTCTCTCGACCCCGGCGCTGGCCCGCACCAACATCTCGCCCATATCCCAGGACAGCTTTA
TGGCCGGCTTCGGCGCGCAGGACACTGGGGTTCAAAGCTCTGGGTTCGCCAGGGGTGGGGGAGGACAGAGAGGACA
GGTGTGGAGAGGCGACAGAGTGTGGGGCTGATGTGACACAGGGCTGAGAGGGTGTCTGAGAGTGGAGAGGTATACCTGGC
GTGACAGACCTGTACTCTTGTTGTGTGTGTGTGTGTGTGCGCGCCACCTCCCACAGCTGGTTCGATGTGCCCTGGGC
TTGGTGACAGCTAGGGTGTAGTGTATGTATGTGCGACGTGCAATTTGATAGTCTCTGTACAGTTTGGAGTTTGTGCTA
GGACCTCGTGTGTGTGTGAAGTTGTTTGTGACCAATGTGCTCTTATGTGCAACAGTGTGTGTGTGTGAGTGTGTAATCTC
GTATGAAGTTGTGTGTGTAATCATCAGGAATGTGTGAGGGCTCTACTTTAGGGTGGCTGTCTCTTTTG

B. Exon 2-11 sequence (with introns included):

[illegible]

Fig. 22

ACTCAGCGNGGTGGGACAGGAGGACCCAAANCCGGTCCANATTTTCCCANAAAGCATGGCTTNGATGCTTGAGGNG
 CGGGCGGGAAGGAGGCAAGGCCCTGAGACTGAACTTCTAGCTGGAGGTTCTGGGGCGGGGCCAGAACGRAAGTGGCG
 CCTGTAGACTGTCAGTTTTCGTTCCATGTTTTTATTGTGCACTGGGAAAGAGTCTTCCCTCCCATACATGAGCG
 ACGTGGTGAGTCCCTCGAGGAGCTTGAAGATTATCCCCCTCCCTGGGAGTCTTGGGCCATCGAGGAGTGGGGCGGTGA
 ACGGAAGGGGATTTTGTCTCTGCCCTCAGCTGTGGGCCCTCTCTTCCAGGAATGTCCAGCGGAATTGTCAATGAG
 GAGAACTTCAAGCAGATTTACTCCAGTCTTCTTCCCTCAAGGAGGTGAGGGGACAAAGGCCAAGGGGAAGCAGTTGTC
 CTTCTCTAGGCTGAGGAGGGGAGGAGTTCTGGAGGAGCTGGGAATGCCAAGGTGATGGGGGTATGGGGAGCTCCTT
 AGAGGGAGGAAGTCTCTCTGTGTGGAAGCAACTTCTCCACACTCACCTCGAGACTCCAGACCTATGCCACTT
 TTTCTCTCAATGCTCTTGACAAACCATGATGGCTCGGTGAGTCTTGGGTGAGTGGGGCAGGTGGGGCAGGGAA
 GCTGTGTTCTCGAGGTTGAGGGCCAGGATCTCCAGGCCAAACCCAGAGAAGGAGTGTGGGTGAAGAGKACCCGAGGAC
 ACAGCTCCCTNCTGCTCTTCTCCAGGACTTTGTGGCTGGTTGTGCGTGATCTTCGGGGAACGTAGATGACAGG
 CTTAATTTGGGCTTCAACCTGTATGACCTTAACAAGGACGGCTGCATCACCAAGGAGGTGACGGGCACTGAAGGGC
 TGGGGGTCTGTGGCGGTGATGGGGTGGCGTGACAGGGGTGATGGGAGGGAAATGACCCACATATGCCCAACAAG
 AATGGGATCAAGGGAGGCTGGAGGCTCTGAGGAAGGATCCTCTCTCTCTTGGCCCTAACAGGAATGCTTGCATCA
 TGAAGTCCATCTATGACATGATGGCAAGTACACGTACCTGCACTCCGGGAGGAGGCCCAAGGGAACACGTGGAG
 GACTTCTCTCAGGACTCTGGGAGTGGGTATGGCTGGAGGGCCCTGGAGTGAAGGGAAGAGGCCAAGAACAACGACAGG
 AGCTCACTGAGTCTCTGTCTGTGCTCTCTTGCATCCTCTGTCTCTCCGTGCTCCGTCGACCACTTTTCGAGAAGA
 TGGACAGAAACAAGGATGGTGTGGTGAACATTGAGGAATTCATGTAGTCTTGTGAAAAGGTACAGCTCTGCCCTC
 TACATTTACCTGACCTGGACTCAGGCCCTGATTTAGTAATGCAGGGAAGAGCTTCTTGGGAAGAATACCCACTTCCC
 ACCTCACCCCATATTTCAATCCTATTCTTTTGGGAGGCTTACCCCTTCCCTACCTCAGGTCTCTCTGGGCATCT
 CCTTCTCTGTGCTTTTGAATGTCCCCGTCTGTGACTCAAGTGTCCCTCTCACTGTCTCTGATAAAGCTCCTCTCTCT
 TTTCTCTCTTCAATCTGCTCTGCTCAGATCATGGCCACAGGATGAGAACATCATGAGGTCCATGCACTCTTTTGAC
 AATGTCACTAGCCCCAGGAGAGGGGGTCAAGTGTCTTCCGGGGGACCATGCTTAACCTAGTCCAGGCGGACCT
 CACCCCTTCTTCCAGGTCTATCTCCTATCCTACGCCCTCCTTGGGGGCTGGAGGGATCCAAAGAGCTTGGGGATTGAG
 TAGTCCAGATCTCTGAGCTGAAGGGGCCAGAGAGTGGGCAGAGTGCATCTCGGGGGGTGTTCCCACTCCCAACAG
 CTTCTCACCCCTTCTCTGCCCTGACACCCAGTGTGAGAGTGCCTCCTGTAGGAATGTAGCGGTTCCCCACCTCTCA
 CCCCTACTCTAGAAACACACTAGACAGATGTCTCTGCTATGTGTCTCTCCCATCTCTGACCTCATAAACATTTTCC
 CTTAAGACTTCCCTCTCAGAGAGAATGCTCCATCTTGGCACTGGCTGGCTTCTCAGACCAGCCATTGAGAGCCCTG
 TGGGAGGGGACAGAAGTATATAGGGAGAAATCTTGGGCTGAGTCAATGGATAGTGCTTAGRAGGTGGCTGGGGTT
 GAGAAATAGAAGGGCTTGGACAGATTATGATTGCTCAGGCATACCAAGTTATAGCTCCAAGTTCCACAGGTCTGCTAC
 CACAGGCCAATCAAAATATAAGTTTCCAGGCTTTGAGAGAACCTTGTCTCTTAGAAATGCCCCAGAAATTTTCCAC
 ACCCTCTCGTATTCATGGAGAGCTGGGGCCAGATATCTGGCTCATCTTGGCATGTCTCTCTCTCTCTCTCTCTCT
 TGCATGTGTTGGTGGTGGTGTGGTGGGGGAATGTGGATGGGGATGTCTCTGATGCTTCCCAAAATTTTCACTC
 CACCCTCTTGCCTATCTGCTGGTGTGGGGGCTATGACTGTGAGTTTGTGTTTCCCATGTTCTCTATAGACTTGGG
 ACCTTCTCAGCTTGGGGCTTATCACTTCCCAAGTGGATGCTTGAAGGAGAGGGAGGAGGGAGGGAGGAGCAT
 GCATCTGAACCCAGTGTGGGGGCTTCACTAGAAATCTTCAATCAACCTGGGCTCTCCCCACCCCAAGTATACCC
 TCTCAGTCTCTAGGCTCTTCTTCTGCTGACTCAATCTACCCAGAGATGCCCTTAGCACACTTAGAGGGCAGGG
 ACCATAGGACCCAGGTTTCAACCCCATTTGTGAGCAACCCAGCCCTTGGGCCACCCCTTAGCACACTCTGCTGCTCA
 TTTAGCTTACCTCCAGTTGGCCAGAACTGTGAGGGAGAGGCCCCAGAGAGCCCCCTTCCCATCAGAAGACTGTT
 GATGCTTTTGCATTTTGGGCTCTCTATATATTTTGAAGTAAGAAATATACAGATC:TAATAAAACAATGGC
 TATGCCACAGCTGCCCCCTCTGCTCTTGTGCTCTCCCATCAAAATACACAAACCCCTAACGATGACCTGCA
 GCCTTTGTAGATCCCCAGAAAGGTGGCTTTCTTTTCCATAGTTGGGCATACCTTGGCATGAGACTGAGACAGAGGCTC
 TGGAAATGGTTGGAAACCAACCACTCAGGCCCCACATGAATCTCCCTCCCAACAGCTGAGAGAGCAAGGA
 AGGAAGGACAGGACATGATGTCCCAAGAGCTGTGCCAAGCAGCTGTTTTTGTAGTGACATTTTACAGTTGAAT
 CACAGATTTCTAATTTACAGACTTTTGTAGTAAATCTCAAGTGCTTTCTTTTGGGGGCTCTCTTAAGTCTTTCTT
 TTTT

Fig. 22 Continued

>monkey KChIP4 cds = 265

gtcgaccacgcgtccggtgcgctgtggagcggggggagccccgccagccaaatgccaggatcagcatgagagcgttg
actttagtcacaggtctgtcctcacccegggggacgcgcgctttgcagggtgcagctgcgagggaactgctcactttttc
cccttgcaagctctttgtccaaagcctgcagctgtgctacgattctgtaataactccctccactccaaaggggtctggaggc
tgggatgctctgcagcctcagaggATGTTGACTCTGGAGTGGAGATCCGAAGGACTGCAACACAGTGGGTA
TTGTTGTGAT
TATATGTGCATCTCTGAAGCTGCTTCATTGTGCTGGGACTGATTGATTTTTTCGGAAGACAGCGT
GGAAGATGAAC TGGAGA
TGGCCACTGTGAGCATCGGCCCTGAGGCCCTTGAGCTTCTGGAAGCCGAGCAAAATTTACC
AAGAAAGAGCTTCAGATC
CTTIACAGAGGATTTAAGAACAATGCCCCAGTGGTGTGTTAATGAAGAAACCTTCAAAGA
GATTTACTCGCAGTCTT
TCCACAGGGAGACTCTACAACATATGCACATTTTCTGTTCAATGCGTTTGATACGGACCACA
ATGGAGCTGTGAGTTTCG
AGGATTTTCATCAAAGGTCTTTCCATTTTGTCTCCGGGGACAGTACAAGAAAACTCAATTGG
GCATTTAATCTGTATGAT
ATAAATAAGATGGCTACATCACTAAAGAGGAAATGCTTGATATAATGAAAGCAATATACG
ACATGATGGGTAAATGTAC
ATATCTGTCTCAAAGAAGATGCCCCAGACAACACGCTGAAACATTTTTTCAGAAAAATGG
ACAAAAATAAGATGGGG
TTGTTACCATAGATGAGTTCATTGAAAGCTGCCAAAAAGATGAAAACATAATGCGCTCCATG
CAGCTCTTTGAAAATGTG
ATTTAActtgtcaactagatcctgaatccaacagacaaatgtgaactattctaccacccttaaagtcggagctaccactt
ttagcatagattgctcagcttgacactgaagcatattatgcaaacacagctttgttttaataaagcaatccccaaaaga
tttgagtttctcagttataaatttgcatcctttccataatgccactgagttcatgggattgttctaactcaattcactc
tgtgaattattcaaaagttaataagatctgycatagttttattgattcccttagccatgggattattgaggctttcacata
tcagtgatttttaaaataccagtggttttgcctcatttggatgtattcagtcctaggtatttgaatgggttttctaatat
actgacatctgcatttaattccagaaaataaattaaatttcatgctcgaatgctgtaattccatttatactttaagt
aaacaaataagattactacaataaacacatagttccagtttctatggcctccctccocacttctataaaataat
tttatctgggtatttttaaacatttaaaatttatcatcagatcatcgcatatgcctaattatgcctaataaagacttaata
agcattttaaatttccatcatcattatagccaaggcctatatactatataaatttggatttgtttaatctacaggtc
gttttccattgtatcatcaagtggaaagtccaagcggcatcaacaaacaaaggaattgttacagacatcatgcaaaagggtc
aggatattctatcctccagtatattgtaagtgttaataacaagtaactcctaacagcattaaagccaaatctgtcctcttt
ccccgtacttctatcagcagttttatattacaagccttcaggggacaaagaaacttgactaccocctgtctactagg
aacaacaaacagcagcaagcaaaattcactttgaaagcaccagtggttccattacattgacaactactccaagattcagta
gaaaataagtgctcaacaaactaatccagattacaatatgattttagtgcatcatataaattccaacaattcagattatttt
aatcatctcagccacaactgtaaagtgccacattactaaagacacacacatcgctccctgtttgtgaaaaatcacaaa
gaccaagaggtcacagaaggaggaaaatttgcaactgtctttgcaacaataaatacaggatcatcttctgggtgagatag
gatgttgaaagctgcctgctatcaccagtgtagaaaataagagtagtacaatacattgactgaattggccatcgcg
tgtttgtgtaactcaatgtgcacattttgtatttcaaaagaaaaataaaagcaaaaataaattgttwwaammmwaaa
aaaaaaaaaaaa

>monkey KChIP4

MLTLEWSEGLQTVGIVVICAASLKLHLGLIDFSEDSVEDELEMATVHRPEALELLEAQSKFT
KKELQILYRGFKNE
CPSGVNVNEEFKEIYSQFFPQGDSTTYAHFLNFAFDDHNGAVSFEDFIKLSILLRGTVQEKLNW
AFNLYDINKDGYIT
KEEMLDINKAIYDMMGKCTYPVLKEDAPRQHVETFFQKMDKNKGVVTTIDEFIESQCKDENIM
RSMQLFENVII

Fig. 23

>monkey KChIP4 C terminal splice variant cds = 265-966

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gtcgaccacagcgctccgggtgcgtgtggttgcgggggggagcccgccagccaaatgccaggatcagcatgagaggctgg
acttttagtcagggtctgtcctcaccgccgggggacccggtcttgcagggtgcagctgcaggaaactgctcaacttttttc
cccttgcaagttcttggctccaagcctgacgttgctacgattctgtaatctcctccactccaaagggtctggaggc
tgggatgctctcgccagctcagaggATGTTGACTCTGGAGTGGGAGTCCGAAGGACTGCAAAACAGTGGGTA
TTGTTGTGAT
TATATGTGCATCTCTGAAGTGTCTTCATTTCGCTGGGACTGATTGATTTTTTCGGAAGACACGCT
GGAAGATGAACTGGAGA
TGGCCACTGTCAGGCATCGGCCCTGAGGCCCTTGAGCTTCTGGAAGCCCAGAGCAAATTTACC
AAGAAAAGAGCTTCAGATC
CTTTACAGAGGATTTAAGAACGAATGCCCCAGTGGTGTTGTTAATGAAGAAACCTTCAAAGA
GATTTACTCGCAGTTCTT
TCCACAGGGAGACTCTACACATATGCACATTTTCTGTTCAATGCGTTTGATACGGACCACA
ATGGAGCTGTGAGTTTCG
AGGATTTTCATCAAAGGCTTTTCCATTTTGCTCCGGGGACAGTACAAGAAAACTCAATGG
GCATTTAATCTGTATGAT
ATAAATAAAGATGGCTACATCACTAAAGAGGAAATGCTTGATATAATGAAGCAATATACG
ACATGATGGGTAATGTAC
ATATCTGTGCTTCAAAGAAGATGCACCCAGACAACACGTCGAAACATTTTTTCAGGCTGTTT
TCCATTTGTATCATCAAGT
GGAAGTTCAAGACGGCATCAAAACAAAACAAAGATGTTTACAGACATATGCAAAAGGCTCAGG
ATATCTATCTCTCCAGTATA
TGTTAAtgcttaataacaagtaatcctaacagcattaaaggccaaatctgtcctctttccctgacttcttacagcatg
tttatattacaagccattcaggggacaagaaaccttgactacccactgtctactaggaaacaaacaaacagcaagcaaaa
ttcactttgaaagcaccagtggttccattacattgacaactactaccaagattcagtagaaaaatagtgctcaacaacta
atccagattacaatatgatattgtgcatcataaaattccaacaattcagattattttaatcatctcagccacaactgta
aagttgccacattactaaagacacacacatcgctccctggtttgtagaaatatcacaagaccagggctacagaaggag
gaaatttgcaactgtcttggcaacaataatcaggtatctattctggtgtagagataggatgttgaaagctgccctgcta
tcaccagtgtagaaattaagagtagtacaatacatgtacactgaattggccatcgctgtttgtgtgtaaacccaatgtgc
acattttgtatttcaaaaagaaaaataaaagcaaaataaaatgttwawaamwwaaaaaaaaaaaaaaaaaaaaa

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>monkey KChIP4 C terminal splice variant

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MLPLEWESEGLQTVGIVVVICASLKLHLGLIDFSEDSVEDELEMATVRRHPEALELLEAQSKFT
KKELQLILYRGFKME
CPSGVVNEETFKIYISQFFPQGDSTTYAHFLNADFDTDHNGAVSFEDFIKGLSILLRGTVQEKLNW
AFNLIDYINKDGYIT
KEEMLDIMKAIYDMMGKCTYPVLKEDAPRQHVETTFQAVFHCIKWKFKTASNKTRMPTDICK
GGYLSSSIC

```

Fig. 24

KChIP1_1v -----MCAVMGTF-----SSEQTQK-----RKE-----
 KChIP2_9q1 MRGQGRKESLSRDLGSSYDQITGHPPGPYKALKORFKLLPCCGPQALPSVSETLAA
 KChIP3_p19 --MQPAKEVTKAS--DGSELGDLGH--TPESKKEGELKWQRPRLSRQALMRCCLVKWI
 KChIP4_352 ---MLTLEWESEGLQTVGIVVILCAS---LKLHLHLGLGTFDSE-----
 KChIP4_231 ---MLTLEWESEGLQTVGIVVILCAS---LKLHLHLGLGTFDSE-----
 hsnscspara ---HEVESISAQLEEASSTCGFLYAQN-STKRSIKERLMLKLLCS-----

KChIP1_1v -----SKDKLEDELEMTMWCHRPEGLEQLEAQTNETKRELOVLYRGFKNECPS
 KChIP2_9q1 PASLRPHRPRLLDPSSVDDEFELSTWCHRPEGLEQLOEQCTKPTRKELQVLYRGFKNECPS
 KChIP3_p19 LSSTAPQ-----GSDDSSDELELSTVRHOPEGLDOLQAOIKTKKELQSLYRGFKNECPT
 KChIP4_352 -----DSVEDELEMATVRRHPEALELLEAOSKFTKKELQILYRGFKNECPS
 KChIP4_231 -----DSVEDELEMATVRRHPEALELLEAOSKFTKKELQILYRGFKNECPS
 hsnscspara --AAKTSSP---AIONSVDELEMATVRRHPEALELLEAOSKFTKKELQILYRGFKNVRTF

KChIP1_1v GVNNEETPKQTYAOFFPHGDASTYAHFLNFAEDTTOTGSAVKFEDEVTLSTLLRGTVHEK
 KChIP2_9q1 GVNNEENFKQTYSOFFPOGDSSTYATFLNFAEDTNHDSVSFEDEVAGLSVTLRGTVDDR
 KChIP3_p19 GLVDEETPKLYIAOFFPOGDATTYAHFLNFAEDADGNGATHEDEVVGLSILLRGTVHEK
 KChIP4_352 GVNNEETPKQTYSOFFPOGDSSTYAHFLNFAEDTDHNGAUSFEDEVTKGLSILLRGTVQEK
 KChIP4_231 GVNNEETPKQTYSOFFPOGDSSTYAHFLNFAEDTDHNGAUSFEDEVTKGLSILLRGTVQEK
 hsnscspara FETLPSHNSQRSIEK-----

KChIP1_1v LRWTFNLYDINKDGYITKEEMLDIMKAIYDMMGKTYTPVLKEETPROHVDTFFQKMD---
 KChIP2_9q1 LNWAFNLYDLNKDGCITKEEMLDIMKSIYDMMGKTYTPALREEAPREHVSEFFQKMD---
 KChIP3_p19 LKWAFNLYDINKDGYITKEEMLDIMKSIYDMMGKRTYPIGREDAPEHVVERFFQKMD---
 KChIP4_352 LNWAFNLYDINKDGYITKEEMLDIMKAIYDMMGKCTAPVLKEEDAPROHVETFFQKMD---
 KChIP4_231 LNWAFNLYDINKDGYITKEEMLDIMKAIYDMMGKCTAPVLKEEDAPROHVETFFQAMPHCI
 hsnscspara -----

KChIP1_1v ---KMKDGIYTLDEFLESCQEDDNIIMRSQQLFQNM
 KChIP2_9q1 ---RNKDGVAITHEEFLESCQKDENIMRSQQLFDNVI
 KChIP3_p19 ---RNQDGVATTHEEFLACQKDENIMSSQQLFENVI
 KChIP4_352 ---KMKDGIYTLDEFLESCQKDENIMRSQQLFENVI
 KChIP4_231 IKWAKFTASNKTRMTDICKGSGYLSSTIC-----
 hsnscspara -----

Fig. 25

MNGVEGNNELPLANTSTALSALVPEDLDLKQDQLSEETDVTREMAAGEAGAEAGGASPDSEHCDPQLCLRWAEKNGAAGAAAG
 EDEGLDLSSSCKGADPLASVAANDSNKNGQLAGLSPAPKMTLEAGSVALGSSGMPMPKTKVTMTKGAISATTTGGAI
 EAGAAMEKKGVQKEKKAAGGKGDTEPRAPKINCMDSLEALQDLSHVNAQADRAFLQLERKFVGRRAHLMHQRSFTI
 QNI PGFWVTAFRNHQLSPMISGQDEDMRYMINLEVEELKHPRAGCKFKFIQSNPYFRNGLVKEYYERSSSGRVVSLS
 TPIRWHRGQEPQAHIRHNRNGTIPSPFNFWSDHSLLEFDRIAETIKGLWNSNPLQYYIMMGDGPARGRVPRPQVPESPR
 SFRFOSG.

[illegible]

Fig. 26

Rat 1p protein (partial)

LKGARPRVVNSTCSDFNHGSSALHIAASNLCLGAALKLEHGANPALNRKQVPAEVVDPMDMSLDKAEALVAKELRT
 LLEEAVPLSCTLPKVTLPNYDNPGLMLLSALGLRLGDRVLLDGQKTGTLRFCGTTFTEASGQWVGVELDEPEGRKNDGSVG
 GVRYPICPPKQGLFASVSKVSKAVDAPFSSVTSTPRTPRMDFSRVTGKRREHKKKKSSPSSPLGSLQREQGAKAEVGD
 QVLVAGQNRDCAFLWEDRLSKRLLVWH

Rat 1p DNA (partial, coding:1-804)

CTGAAGGGGCGAGGCCAGGGTGGTGAACCTCCACCTGCAGTGACTTCAACCATGGCTCAGCTCTGCACATCGTGCCTC
 GAATCTGTGCCTGGGCGCCGCCAAATGTTTACTGGAGCATGGTCCAAACCCAGCGCTGAGGAATCGAAAAGCAGGTAC
 CAGCGGAAGTGTGCCAGACCCCATGGACATGTCCTTGAACAAGCAGAGGACAGCCCTGGTGGCCAAAGAAATTGCGGACG
 CTGCTAGAAGAGGCTGTGCCACTGTCTGCACCTTCTCTAAAGTCACTACCCAACTATGACAACGTCCCAAGGCAATCT
 CATGCTCAGCGCGCTGGGCTGTGCTTAGGAGACCGAGTGCTCCTCGATGGCCAGAAGACGGGACAGCTGAGGTTCTGCG
 GGACACCGAGTTCGCCAGTGGCCAGTGGGTGGGCGTGGAGCTAGATGAACCGGAAGGCAAGAACGACGGCAGCGTTGGG
 GGTGTCCGGTACTTCATCTGCCCTCCCAAGCAGGGTCTCTTTGCATCTGTGTCCAAGGCTCTCAAGGCGAGTGGATGCACC
 CCCCCTCATCTGTTACCTCCACGCCCCCGCATCCCGGATGGACTTCTCCCGTGAACCGGCAAGGCCCGAGGGAACACA
 AAGGGAAGCAAGTCCCATCTTCCCCATCTCTGGGACAGCTGCAGCAGCGTGAAGGGGCCAAAGCTGAAGTTGGAGAC
 CAAGTCTTGTGGCAGGCCAGAACAGGAGTTGTGCGTTTCTATGGGAAGACAGACTTTGCTCCAGGTACTTGGTATGGCA
 TTGAACGGACAGCCACCGGCAAGCATGACGGCTCTGTGTTCCGGTCTCCGGTACTTTACCTGTGCCCGGAGGCAAGCGG
 GTCTTTGCACCCAGCATCTCGTATCCAGAGGATTGGTGGATCCACTGATCCCCCTGGAGACAGTGTGTGGAGCAAAAAAAGT
 GCATCAAGTGACAATGACACAGCCCAACGCACCTTCACAACAGTCCGAGACCCCAAGGACATTGCATCAGAGAACTCTA
 TCTCCAGGTTTACTCTTCTGCTGCTGTTTCTTGGATGCTGAGGCGGAGATGCACTCTTAGAGACCTGGATACCTTGACA
 CAGAGACAGAGTCCCCCTTAGCATCTCCTGACACAGGAGACCCCAAGTCAACCTAAGATAGAGATTCCCAAGTACACCTC
 CAGATAGAAACCCCGTTAGCCAGCCCTCGATTACTGAGGTCCCATTTATTAACAGATCTCCCATGACGACTCCCCCAAT
 ACAGACCTCATGTTACCCCAAAAGAGATTCCCTGAGTAGCACCTTCAGGCTAGTCCCTGCTCCCTCAGCCCTCAGAGCAGA
 TTTCCCCCAATAAACATTTTCCACATCACCCAAAGGATGCTGACCTCTCCACGACAGGAGCTTCTGAGTTACCAGTGG
 ATTAGAGTCCCATGAATGAAGACCCCCCCCCACCCCGGTTCTCCTTAAGCATAGGTATACCTCCAGAAATAGCCAGGCACA
 TCACATATCCCCATGTAACATCAGTCTCCTCAAAATGGCGTGAGTGACTAGAAAGACCTTATACTCTCCTCTCCTCTCA
 GAGATGCCCTCATTCACTTAAGTCCCTGTTCTCACCCCTGAACAAGACCTTAATTAACCGGCCCATCACTCAATTA
 CAAACACCAAAATTCGCTCGGAAGCATGAATTAAGGACAGCAAGTCTTCTGCCCTCTGCACCTTTGAGAAACCCCCAG
 TGCCCTGTGATGAAGCCACCCACATGGCCACAGTCCCTGTGCTGGCCAAAGGCTCCCAAGAAATTTCTCTATTTTTTAA
 GATAATACCTCCCCCCTTTGGGGGATCCCCAAATTTGGAGACCCCATCTAGAACACTGGGGAGTTCAAAATTCAGAG
 AGAATATATATATATATAATCCCAATTCCTCCATGCTTCCAAGCCCTACAATCTCTAGAAGACCCCAATTTCTAATTC
 CCAGGACTTCCCCTACCAAGTCACAGAATCTTCAAAATCCCAAGGAAATCCCAAACTTAAGATACCAATCCCAAAACCTC
 AGGAAATCCCCCAACACAAAGTCCCTTAGGACCGGAGGAAGAACTGTTGCCAGGAGAACAATCCCAAGGCTCTCAGGGCA
 TCTCAAACTGACTCCAGGACACAGGAGACCCCAACAGAAAGTCCCATCTTTGGAGCAAGGATAGGACTCTAATACCC
 TTAGTCCATGGATCTTTAATTTCCCAACCTCCAAACTCCATGGGCCCCACCTCAAGGGAACCCCAAGATCCCAATCTC
 TGATAACTAATATGTGACAGGGCCCAAGGCTCTAACAGGACCCCAAAATCATGGAGTCCCTACTTCAATCTACCTTCTGGT
 CACAGGTCCAAGACCTAAATCTTGAGTCTATTGGCCCCAAAGGACTTCACAGCACCTGGGCCAGACTAACAGCTGAGGGA
 GAACCTGAGGGCCCCGTGGTCCAGAGCAGACTGGGGCCCTGACCACCAAGGACAGCTACAGACTGCCCTTCACTGCA
 TGTCCCTAAACTCAGCATGACTCTGTCTCTTCAATAAAGACGTTTCTATGGCAAAAAAAAAAAAAAAAAAAAAAAAAA
 AAA

Rat 7s Protein (partial)

ADSTSRWAEALREISGRLEAMPDSGYPAYLGARLASFYERAGRVKCLGNPEREGSVSIVGAVSPPGGDFSDPVTSATLG
 IVQVFWGLDKKLAQRKHFPSVNWLLISYSKYMRALEDYDDKHFEFVPLRKAKEILQEEDLEAIEVLVKGASLAETDKI
 TLEVAKLIKDDPLQNGYTFYDRPCFPYKTVGMLSNMISFYDMARRAVETTAQSDNKITWSIIREHNGEILYKLS SMKFK
 DPVKGEAKIKADYAQLLEDQMNAFRSLED

Rat 7s DNA (partial, coding: 1-813)

GCTGACTTACCTCTAGATGGGCTGAGGCCCTCAGAGAAATCTCTGGTCGCTTAGCTGAAATGCCTGCAGATAGTGATA
 CCCTGCATACCTTTGGTGCCCGACTGGCTCTTCTTCTATGAGCGAGCAGGCAGAGTGAATGTCTTGGAAACCTCGAGAGAG
 AAGGGAGTGTGACAGCTTTAGGAGCAGTTTCTCCACCTGGTGATTTTTCTGATCCAGTCACTCTGCTACTCTGGGT
 ATTGTTCCAGGTGTTCTGGGGCTTGGATAAAGCAGTCTCAGCGCAAGCAGCTTCCCGTCGCTCACTGGCTCATAGCTA
 CAGCAAGTACATGCGCGCCCTGGACGAGTACTATGACAAACACTTCACAGAGTTCGTGCCTCTGGAGACCAAAGCTAAGG
 AGATTCTCGAGGAAGAGGAGGATCTGGCGGAAATCGTGACGCTCGTGGGAAAGGCGTCTTTAGCAGAGACAGATAAAATC
 ACCTGGAGGTAGCAAAACTTATCAAGATGACTTCTTCAACAAATGGGTACACTCTTATGACAGGTTCTGTCCATT
 CTATAAGACGGTGGGGATGCTGTCTCAACATGATTTCACTTCTATGATATGGCCCGCGGGCTGTGGAGACCAACCGCCAGA
 GTGACAAATAAGATACATGTGCTTCAATTCGTCGAGCACATGGGGGAGATTCTCTATAAACTTTCCCTCAATGAAATTCAG
 GATCCAGTGAAGGATGGCGAGGCAAGATCAAGGCCGACTACGCAAGCTTCTTGAAGATATGCAAGACGCATCCGCTAG
 CCTGGAAAGATTAGAATCTGTGACTTCTCTCTCTCTTCCGACGCTCATATGTGTATATTTTCTGAAATTTCTCATCTCCA
 ACCCTTTGCTTCCATAATTGTGCAGCTTTGAGACTAGTGCCTCGTGCCTTCTCGTTCATTTTGTCTGTTCTTTGGTAGGCT
 TTATAAAACACACATTTCTCTGCTCCGCTGTCTGAAGGAGCTCTGACCTTTGTCTGAAGTGTGTAATGTAGTGCATATG
 ATACACAGTGTAAACATACACATTGTAACATATACGTTCTGTAACCTTGATGTAAAGTGACTACCCCTTCCCTCTCTCC
 AGTAACTGTAAACAGGACTACTGCATGTCTCTATTGGGGATGGAAGGCCAGATCTCCATACCGTGAACAGGTACATAA
 GGAACCTAGACCACTTGCAACTTAGTGTTTGTGTAGTAACCAATTTTGCAGGAAGATATTTCCATTTAAAAACAAAGATT
 AATGTTCCAAATTTATTGTAGCTTCCCCAGTATCAATCAGGACTGTTTGTGGCGCACTTGGGAACATATTTGTGTTTCTTAA
 CAGACGTTTGCAGGCTGAACGTAAATAGATAAAATCAGTTCCCTCTGAAAGTGTGAAAGTAAAGAGAGCTAGGTGGTCA
 GACTTAAATGTACATCGCTGTGTTTAAAGCATATTTTATTCTAGAGATTTAATATCAAGGACTTTTATATACTCAAT
 TACTAGGAAATCTTTTTTAAAGTACAATTTAAAAATCATTGAAATGTGATCCACATCATAGCCATTTTCTCTATATTTA
 GTCAGATGAGCTCAGAGTGGGGAGGGGTGGGTAGAAATACCACAAGGACACGCGAGTGCCTGCAGGCAGTGTGGCCG
 GGGCCAGAGCGGCATTGTTTTACAGAGGTACGTGTGTGGCGTGTGTGTTTCTGTTGACACTCTGAAAAACAGCAAGCT
 TACCAGTTCAGGAAATATTTTGTGTTTCTTCTCACTGGCTCAGAAAGCTCTCAAAGTACCTGGTCCCTGAAGCTTCTCTAT
 CTGTGTTAATAGAGACGAGAGAGGTTCTTTAAATTTAACTGGTGACAAAAACAAAGAAAAAGATCGAATTTTGTCTGTC
 TGTGTTTGGTGTGTTTAAATAATAATTCATATTTGACATAACGAGGCTCGCTCTGAGAGCTTGGAGATCGTGCCTCTCT
 TCACTCTCTCGGGTGATATGCTGGCGCATGTACTCTTCTCAGGAGGGGAAGGGGATGAACATGTGCTAACACTCTCA
 GTACACAAGCGTAAACGACAAAGTATTTATTTTAAAGCTTGGTATGTTGTTTAAATTTATAGTGGTGCATTTCTTATGGT
 CTTTGTGGGTAGACATAGTATACACTCAGATGTAAATGTGTAATCCTTGCTAGTGCATGTCTACACGATAGACTGCTATT
 CAAGAAGGATATCTTCCACATAACAAATTTAAAACTATTAAATCAGATATGGAATATGCAATGACTTTGTGAGAGGTGG
 ATTTAACGGTGTGCTTAACTGATTTGCTTCCCAATATGGCTTCGTATCCAGAAGCCTGACTAGTGGAGATGAGAAAGCT
 TCAAAACCTGTCTGCTACACCTACCGCAACCTAGGCTTGTGATCAGAATGAATGATCCCAAGAACTACTTGAACCAAG
 TGTGTTTGTGTCTCGGATTTGAGATGTGCGTCTTCTCTCTCTGAGACTGTTGATGTATGAGTGTGAAGAAGTTACA
 GAAACCAACCTCAGATTTTACGGGTAACTTTCCCTCTGCCACACCTAGAGTTCAGATTTGCTCACTGATAGTGTCTTCT
 TTCTGAAGGATGTGTTAAAAATATAGCAGTCTTTTAAAGATATGACAGTCTCTATTATTTGTGCTGTGCTCGGCTTCA
 AGTGCAGCCGGTTAAACAGTTTCTATGTATTTTTCCAGTGTAAATCTCATACCTATGCCCTTTGGAAGGCTCCATCC
 TGAACCAATGAATAGAAGAGGCTTATAAAATGCTCCTTATGCTTCAAGATTTCATATTTATGTTATGTTAAGAGTAATGTAT
 AATTATTAATCTATGAAAAATAAAAGTGGAATTTAAATTAAGAGATC

Fig. 29

Rat 29x protein

ARLPAPEHARQQPLSLGPEPGSSARVPVPGVASRRQPRGGKPPSGDGLSEGPSFREFLLHARGEAGLHRQSGRVPHTGTAY
 FADEPTEAQAPGGFCVSPSLLGVRWPACATRTPGSLPLSPSAQPRTLWPPTPAGPSSRMVARNQVAADNAISPASEPRR
 RPEPSSSSSSSPAAPARPRPCVVPAPAGDTHFRTRFSHSDYRRITRTRTSALLDACGFYWGPLSVHGAHERLRAEPVGT
 FLVRDSQRNCFFALSVMASGPTTSIRVHFQAGRFLHDSRETDFCLFELLEHYVAAPRMLGAPLRQRRVRPLQELCRQ
 RIVAAGRENLARIPLNPVLRDYLSSFPFQI

Rat 29x DNA (coding: 433-1071)

GCACGGCTCCCGGCCCCGGAGCATGCGGACAGCAGCCCCCTCCTCtCCGGCCCTGAGSCCGGATCGTCCGCCCGGGTTCC
 AGTTCCTCCGGCGTGGCCAGTAGGCGGCGAGCCGCGAGGCGGCAAGCCACCCAGCGGGGACGGCTTGGAGTCGGGCCCTCTC
 CACGCCCCCTTCTCCACGCGCGCGGGGAGCGAGGGCTCCACCGCCAGTCTGGAAGGGTTCCACATACAGGAACGGCCTAC
 TTCGCAGATGAGCCACCGAGGCTCAGGCTCCGGGCGGATTTCTGCGTGTACCCCTCGCTCCTTGGGGTCCGCTGGCCGGC
 CTGTGCCACCCGGAGCCCGGCTCACTGCCTCTGTCTCCCCCATCAGCGCAGCCCGGACCGTATGGCCACCCCTCCAG
 CTGGCCCCTCGAGTAGGATGGTAGCAGTAACAGGTGGCAGCCGACAAATGCGATCTCCCGGCATCAGAGCCCCGACGG
 CGGCCAGAGCACTCTCGTCTCTGCTCTCGCTCCGCGCGGCCCCGGCGCGTCCCCGGCCCTGCCCCGTTGGTCCCGGG
 CCGGGCTCCGGGCGACACTCACTTCCGCACCTTCCGCTCCCACTCTGATTACCGGGCGCATCACGCGGACCCAGCGCTCTCC
 TGGACGCTCGGGCTTCTACTGGGGACCCCTGAGCGTGCATGGGGCGCACGAACGGCTCGGTGCCAGGCCGCTGGGCACC
 TTCTTGGTGCAGCAGTCCGCGGAACTGCTTCTTCGCGCTCAGCGTGAAGATGGCTTCGGGCCCCACGAGCATTCCG
 TGTGCACTTCCAGGCGGGCCGCTTCCACCTGGACGGCAGCCGCGAGACCTTCGACTGCCTCTTCGAGCTGCTGGAGCACT
 ACGTGGCGGGCCGCGCGCATGTTGGGGGCCCCACTGCGCGCAGCGCCGCTGCGGCCGCTGCAGGAGCTGTGTGCCAG
 CGCATCGTGGCCGCGTGGGTCGCGAGAACCTGGCAGCATCCCTTTAAACCGGTACTCCGTGACTACCTGAGTTCCCTT
 CCCCTTCCAGATCTGACCGGCTGCCGCCGTCGCCGACGATTAAGTGGGAGCGCTTATTATTCTTATTATTAAATTATT
 ATTATTATTTCGGGAACACGCTGGGAGCCCTCCCGGCTAGGTTCGAGGGAGTGGGTGTGGAGGGTGAATGCCTCCCACT
 TCTGGCTGGAGACCTTATCCCGCTCTCGGGGGCCCTCCCTCCTGTGCTCCCTCCGGTCCCCCTGGTTGTAGCAGCT
 TGTGTCTGGGGCCAGGACCTGAATCCAGCCTACCTCTCCATGTTTACATGTTCCAGTATCTTTGCACAAACAGGGG
 TGGGGGAGGGTCTCTGGCTTCATTTTCTGCTGTGCAGAAATTTCTATTATTTTACATCCAGTTTAGATAATAAA
 CTTTATTATGAAGTTTTTTTTTTAAAGAAAAA

Fig. 30

Rat 25r DNA (coding 130-

GGCACGGCTCCCGGCCCCGGAGCATGCGCGACAGCAGCCCCGGAACCCCAAGCCGCGGCGCCCCGGTCCCGCCGCCAGC
GCAGCCCCGGACGCTATGGCCCCACCCCTCCAGCTGGCCCCCTCGATAGGATGGTAGCACGTAACCAAGGTGGCAGCCGACA
ATGCGATCTCCCCGGCATCAGAGCCCCGACGGCGGCCAGAGCCATCTCGTCTCTCGTCTTCGCTCTTCGCGCGGCGCCCCG
GCGCGTCCCGGCCCCGCGGTGCCCGGTGGTCCCGGCCCCGGCTCCGGGCGACACTCACTTCCGCACCTTCCGCTCCCACTCTGA
TTACCGCGCATCACGCGGACCAAGCGCTCTCCTGGACGCTCGGGCTTCTACTGGGGACCCCTGAGCGTGCATGGGGCGC
ACGAACGGCTGCGTGCCGAGCCCCGTGGGCACCTTCTTGGTGCGCGACAGTCCAGCGGAACCTGCTTCTCGCGCTCAGC
GTGAAGATGGCTTCGGGCCCCACGAGCAATTCGTGTGCACTTCCAGGCCGCGCGCTCCACCTGGACGGCAGCCGCGAGAC
CTTCGACTGCCTCTTCGAGCTGCTGGAGCACTACGTGGCGGCGCGCGCCGCATGTTGGGGGCCCCACTGCGCCAGCGCC
GCGTGCGGCGCGCTGAGGAGCTGTGTGCCAGCGCATCTGGCGCCGCTGGGTGCGGAGAACCTGGCAGCATCCCTCTT
AACC CGTACTCCGTGACTACCTGAGTTCTTCCCCCTCCAGATCTGACCGGCTGCCGCGCTGCCCGCAGCATTAAGTGG
GAGCGCCTTATTATTCTTATTATTAATTATTTATTTTCTGGAACCAAGTGGGAGCCCTCCCCGCCTAGGTCTGGAGG
GAGTGGGTGTGGAGGGTGAGATGCCTCCCACTTCTGGCTGGAGACCTTATCCCGCCTCTCGGGGGGCCCTCCCTCTCGT
GCTCCCTCCCGGTCCCCCTGGTTGTAGCAGCTTGTGTCTGGGGCCAGGACCTGAACCTCACGCCTACCTCTCCATGTTTA
CATGTTCCCAATATCTTTGCACAAACAGGGGTGGGGGAGGGTCTCTGGCTTCAATTTTCTGCTGTGCAGAAATATCTAT
TTTATATTTTACATCCAGTTTAGATAATAAACTTTATATGAAAGTTTTTTTTTAAAAAAAAAAAAAAAAAAAA

Fig. 31

Rat 5p protein

MPSQMEHAMETMLTFHRFAGEKNYLTKEDLRVLMEFEFFGFLENQKDPLAVDKIMKDLQCRDGVGFQSFSLVAGLI
IACNDYFVVMKQKK

Rat 5p DNA (coding: 52-339)

CTTCCAAAGACTGCAGCGCCTCAGGGCCAGGTTTCAACAGATTCTTCAAAATGCCATCCCAAATGGAGCATGCCATGGA
AACCATGATGCTTACATTTACAGGTTTGCAGGGGAAAAAACTACTTGACAAAGGAGGACCTGAGAGTGCTCATGGAAA
GGGAGTTCCCTGGGTTTTTGGAAAATCAAAAGGACCCCTCTGGCTGTGGACAAAATAATGAAAGACCTGGACCAGTGCCGA
GATGGAAAAGTGGCTTCCAGAGCTTCTATCACTAGTGCGGGGGCTCATCATTTGCATGCAATGACTATTTTGTAGTACA
CATGAAGCAGAAGAAGTAGGCCAACTGGAGCCCTGGTACCCACACCTTGATGCGTCCTCTCCCATGGGGTCAACTGAGGA
ATCTGCCCCACTGCTTCCTGTGAGCAGATCAGGACCCTTAGGAAATGTGCAAATAACATCCAATCCAATTCGACAAGCA
GAGAAAAGAAAAGTTAATCCAATGACAGAGGAGCTTTCGAGTTTATATTGTTTGCATCCGGTTGCCCTCAATAAGAAAG
TCTTTTTTTTTAAGTCCGAAAAA

Fig. 32

Rat 7q protein

MAYAYLFKYIIIGDTGVGKSCLLQLFTDKRFQPVHDLTIGVEFGARMITIDGKQIKLQIWDTAGQESFRSITRSYYRGAA
 GALLVYDITRRDTFNHLTTWLEDARQHSNSNMVIMLIGNKSDLSESRREVKKEEGEAFAREHGLIFMETSAKTASNVEEAF
 INTAKEIYEKIQEGVFDINNEANGIKIGPQHAATNASHGGNQGQAGGGCC

Rat 7q DNA (coding 1-639)

ATGGCGTACGCCTATCTCTCAAGTACATCATCATCGGCACACAGGTGTTGGTAAATCGTGCTTATTGCTACAGTTTAC
 AGACAAGAGGTTTCAGCCGGTGCAATGACCTCACAAATTGGTGTAGAGTTGGTGCCTCGAATGATAACCATTTGATGGGAAAC
 AGATAAACTCCAGATCTGGGATACAGCAGGGCAGGAGTCCTTTCGTTCTATCACAAAGGTCATATTACAGAGGTGCAGCG
 GGGGCTTTACTAGTGTATGATATTACAAGGAGAGACAGCTTCAACCATTGACAACTGGTTAGAAGACGCCCGTCAGCA
 TTCCAATTCCAAACATGGTCATCATGCTTATTGGAAAATAAAAGTGACTTAGAATCTAGGAGAGAAAGTGAAGGAAAGAAAG
 GTGAAGCTTTTGCACGAGAGCATGGACTTATCTTCATGGAACCTTCGCCAAGACTGCTTCTAATGTAGAGGAGGCATTT
 ATTAACACAGCAAAAGAAATTTATGAAAAATCCAGAAGGGGTCTTTGACATTAATAATGAGGCAACCGCATCAAAAT
 TGGCCCTCAGCATGCTGCTACCAATGCATCTCACGAGGCAACCAAGGAGGCAGCAGGCAGGGGAGGCTGCTGCTGA

Fig. 33

Rat 19r protein

MVLLKEYRVLPSVDEYQVGQLYSVAEASKNETGGGEGVEVLVNEPYEKDDGEKGQYTHKIYHLQSKVPTFVRMLAPEG
 ALNIHEKAWNAYPYCRTVITNEYMKEDFLIKIETWHKPLDLGTQENVHKLEPEANKHVEAIYIDIADRSQVLSKDYKAED
 PAKFKSIKTGRGPLGNWKQELVNQKDCPYMCAYKLVTVKFKWGLQNKVENFIHKQEKLFTNFHRQLFCWLDKNVDLT
 MDDIRRMEEETKRQLDENRQKDFVKGMTADD

Rat 19r DNA (coding 1-816)

ATGGTGTGCTCAAGGAATATCGGGTCATCCTGCCTGTGTCTGTAGATGAGTATCAAGTGGGGCAGCTGTACTCTGTGGC
 TGAAGCCAGTAAAAATGAAACTGGTGGTGGGAAGGTGTGGAGGTCTCTGGTGAACGAGCCCTACGAGAAGGATGATGGCG
 AGAAAAGGCCAGTACACACACAAGATCTACCACTTACAGAGCAAAGTTCCACGTTTGTTCGAATGCTGGCCCCAGAAGGC
 GCCCTGAATATACATGAGAAAGCCTGGAATGCCTACCCCTTACTGCAGAACCGTTATTACAAATGAGTACATGAAGGAAGA
 CTTTCTCATTTAAAAATTGAAACCTGGGCACAAGCCAGACCTTGGCACCCAGGAGAATGTGCATAAACTGGAGCCTGAGGCAT
 GGAAACATGTGGAAGCTATATATATAGACATCGCTGATCGAAGCCAAGTACTTAGCAAGGATTACAAGGCAGAGGAAGAC
 CCAGCAAAATTTAAATCTATACAAACAGGACGAGGACCATTGGGCCCGAATTGGAAGCAAGAACTTGTCAATCAGAAGGA
 CTGCCCATATATGTGTGCATACAAACTGGTTACTGTCAAGTTCGAAGTGGTGGGGCTTGCAAGACAAAGTGGAAAACCTTTA
 TACATAAGCAAGAGAAGCGCTCTGTTACAAAACCTTCACAGGCAGCTGTTCTGTGGCTTGATAAAATGGGTTGATCTGACT
 ATGGATGACATTCGGAGGATGGAAGAAGAGACGAAGAGACAGCTGGATGAGATGAGACAAAAGGACCCCGTGAAAGGAAT
 GACAGCAGATGACTAG

Fig. 34

Monkey KChIP4c (jlkxa053c02) DNA sequence (CD: 122-811)

CGCTCTCCTCCTCCCTTTCTCTAGCAGTAGCCTTCTTAATGTAGTTTAAATGGCTTTACAAAGAAAGCCAGGCAGAGGAG
 CACTTCTCAGTGGCTGTGGTTCGGACCATGACCTAGCTGACCATGAACTTGGAAAGGCTTGAATGATAGCAGTTCTGATC
 GTCATTGTGCTTTTGTGTTAAATATTGGAACAGTTTGGGCTGATTGAAGCAGGTTTAGAAGACAGCGTGGAAAGATGAAC
 GGAGATGGCCACTGTGACAGCATCGGCTGAGGCCCTTGAGCTTCTGGAAGCCAGAGCAAAATTTACCAAGAAAGAGCTTC
 AGATCCTTTTACAGAGGATTTAAGAACGAATGCCCAAGTGGTGTGTTAATGAAGAAACCTTCAAAGAGATTACTCGCAG
 TTCTTTCCACAGGAGACTCTACAACATATGCACATTTCTGTTCATTCGCTTTGATACGGACCAAAATGGAGCTGTGAG
 TTTCGAGGATTTTCATCAAGGCTTTCCATTTTCTCCGGGGGACAGTACAAGAAAACTCAATTGGGCATTTAATCTGT
 ATGATATAAATAAAGATGGCTACATCACTAAAGAGGAAATGCTTGATATAATGAAAGCAATATACGACATGATGGGTAAA
 TGTACATATCCTGTCTCAAAGAGATGCACCCAGACAACACGTCGAAACATTTTTTCAGAAAAATGGACAAAAATAAGA
 TGGGGTGTGTACCATAGATGAGTTCATTGAAAAGCTGCCAAAAGATGAAAACATAATCGCGCTCCATGCAGCTCTTTGAAA
 CACTTTTAGCATAGATTGCTCAGTTTCACTGAATCCAACAGACAAATGTGAACATTTCTACCACTTTAAAGTCCGGAGCTAC
 TACTCTGTAATATTCAAAGTAATAGAATCTGGCATATAGTTTATTGATTCCTTAGCCATGGGATTATGAGGCTTTTC
 ACATATCAGTGATTTTAAATACCAGTGTTTTGTGCTACTCATTTGTATGTATTCAGTCTTAGGATTTTGAATGGTTTTC
 TAATATACTGACATCTGCATTTAATTTCCAGAAATTTAAATTAATTTTCATGTCTGAATGCTGAATTCATTATATACT
 TTAAGTAAACAAATAAGATTACTACAATTAACACATAGTCCAGTTTCTATGGCCCTTCACTTCCCACTCTTATAGAA
 ATTAATTTTATCTGGTATTTTAAACATTTAAAAATTTATCATCAGATATCAGCATATGCGCTAATTATGCTCAATGAAAC
 TTAATAAGCATTTAATTTTCCATCATACATTATAGTCAAGGCCATATATACTATATATAATTTTGGATTGTGTTAATCTTA
 CAGCGTGTTCATTTGTATCATCAAGTGGAGTTTCAAGACGGCATCAAAACAAAACAGGATGTTTACAGACATATGCAA
 AGGGTCAGGATATCTATCCCTCCAGTATATGTTATATTACAAGCCATTTCAGGCACAAAGAACCTTGACTACCCCACTGTCT
 CTCTTTCCCTGACTTCCCTTACAGCATGTTTATATTACAAGCCATTTCAGGCACAAAGAACCTTGACTACCCCACTGTCT
 ACTAGGAACAAACAAACAGCAAGCAAAATTCACCTTTGAAAGCACCAGTGGTTCATTATGACAACTACTACCAAGAT
 TCAGTAGAAAAATAAGTGCTCAACAACATAATCCAGATTACAATATGATTATAGTCATCAAAAATTCACCAATTCAGATT
 ATTTTAAATCACCTCAGCCACAACATGTAAGTTGGCCACATTACTAAGACACACACATCGTCCCTGTTTGTAGAAATAT
 CACAAGACCAAGAGGCTACAGAAGGAGGAAATTTGCACTGTCTTTGCAACAATAAATCAGGTATCTATTCTGGTGTAG
 AGATAGGATGTTGAAAGCTGCCCTGCTATCACCAAGTGTAGAAATTAAGAGTAGTACAAATACATGTACACTGAAATTTGCC
 ATCGCTGTGTTGTGTAAGCTCAATGTGCACATTTGTATTTCAAAAAGAAAAATAAAGCAAAATAAAATGTTTATAAC
 TCTAAAAA

Monkey KChIP4c protein sequence

NNLEGLEMIIVLIVVLVKLLBQFLIEAGLEDSVEDELEMATVVRHPEALELLEAQSKFTKKELQILYRGFKNECPSG
 VVNEETTFKEIYSQFFPGQDSYTHAFLFNAPFDTHNGAVSFEDFIKGLSILLRGTVQEKLNWAFNLVDINKDGYITKEEM
 LDIMKAIYDMGKCTYPVLKEDAPRHVETTFQKMDKNKGVVTTDEFIESQKDNENMRSMQLFENVFI.

Fig. 35

Monkey KChIP4d (jlkx015b10) DNA sequence (CD:64-816)

GTGACAGACGCCCTGGCCGGTGGACTCCTGAGTCTTACTCCTGCACCCCTGCGTCCCCAGACATGAATGTGAGGAGAGT
GGAAAGCATTTTCGGCTCAGCTGGAGGAGGCCAGCTCCACAGGCGGTTTCTGTATGCTCAGAACAGCACCAGCGCAGCA
TTAAAGAGCGGCTCATGAAGCTCTTGCCTTGCTCAGCTGCCAAAACATCGTCTCTGCTATTCAAACAGCGTGGGAAGT
GAACGTGGAGATGGCCACTGTGCAGGCATCGGCCTGAGGCCCTTGAGCTTCTGGAAGCCCAGAGCAAAATTTACCAAGAAAGA
GCTTCAGATCCTTTACAGAGGATTTAAGAACGAATGCCCCAGTGGTGTGTGAATGAAGAACCTTCAAGAGATTTTACT
CGCAGTTCTTTCCACAGGGAGACTCTACAACATATGCACATTTTCTGTTCAATGCGTTTGATACGGACCACAATGGAGCT
GTGAGTTTCGAGGATTTTCATCAAAGTCTTTCCATTTTGCTCCGGGGGACAGTACAAGAAAACCTCAATTGGGCATTTAA
TCTGTATGATATAAAATAAGATGGCTACATCACTAAAGAGGAAATGCTTGATATAATGAAGCAATATACGACATGATGG
GTAATGTACATATCCTGTCTCTCAAAGAAGATGCACCCAGACAACACGTGCAAAACATTTTTTCAGAAAATGGCAAAAAT
AAAGATGGGGTGTGTACCATAGATGAGTTTCATTGAAAGCTGCCAAAAGATGAAAACATAAATGCGCTCCATGCAGCTCTT
TGAAAATGTGATTAACTTTGTCAACTAGATCCGAAATCCAAACAGACAAATGTGAACATATTTCTACCACCTTTAAAGTCGGA
GCTACCACCTTTTAGCATAGATTGCTCAGCTTGACACTGAAGCATATTATGCAAAACAAAGCTTTGTTTTAATATAAGCAAT
CCCCAAAAGATTTGAGTTTCTCAGTTATAAAATTTGCATCCTTTCCATAATGCCACTGAGTTCATGGGATGTTCTGACTCA
TTTCATACCTCTGTGAATATTTCAAAGTAAATAGAATCTGGCATATAGTTTTATTTGATTCTTAGCCATGGGATTTATTGAGG
CTTTTCATATACAGTGATTTTAAAAATACCAGTGTTTTTTGCTACTCATTTGTATGATTTCAGTCTTAGGATTTTGAATGG
TTTTCTAATATACAGCATCTGCACTTTAATTTCCAGAAATTAATTAATTTTCATGTCTGAATGCTGTAATTTCCATTTAT
ATACTTTAAGTAAACAAATAAGATTACTACAATTAACACATAGTTCAGTTCATGTGCTATGCGCTTCACTTCCACCTTCTAT
TAGAAAATTAATTTTATCTGGTATTTTAAACATTTAAAAATTTTATCATCATAGATATAGCATATGCGCTAATTTAGCTAAT
GAACTTTAATAAGCATTTAATTTTCCATCATACATATATAGTCAAGGCCATATATACATATATAAATTTTGGATTTGTTTAA
TCTTACAGGCTGTTTTCCATTTGTATCATCAAGTGGAAGTTCAAGACGGCATCAAAACAAAACAGGATGTTTACAGACATA
TGCRAAGGGTCAGGATATCTATCTCCAGTATATGTTAATGCTTTAATAACAAGTAATCTTAAACAGCATTAAGGCCAAAT
CTGTCCTCTTTCCCTGACTCTCTTACAGCATGTTTATATTACAAGCCATTTCAGGGACAAAGAAACCTTGACTACCCAC
TGCTCTACTAGGAACAACAACAACAGCAAGCAAAATTCACCTTTGAAAGCACCAAGTGGTTCATTTACATTGACAACTACTACC
AAGATTTCAGTAGAAAAATAGTGCTCAACAACATACTCAGATTACAATATGATTTAGTGCATCATAAAAATCCAACAATTC
AGATTATTTTTTAATCACTTCAGCCACACAGTCTAAAGTTGCCACATTACTAAAGACACACACATCGTCCCTGTTTTGTAGA
AATATCACAAAGACCAAGAGGCTACAGGAAGGAGGAAATTTGCAACTGCTTTTGCACCAATAAATCAGGTATCTATTCTCG
TGATAGATAGGATGTTGAAGCTGCGCTTGCTATCCACAGTGTAGAAATTAAGAGTAGTACAATACATGTACACTGAAAT
TTGCCATCGCGTGTGTTGTGTAACCTCAATGTGCACATTTTGTATTTCAAAGAGAAAAATAAAGCAAAAATAAATGTTA
AAAAA

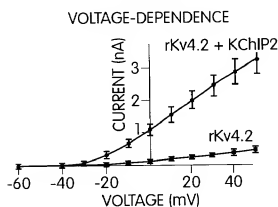
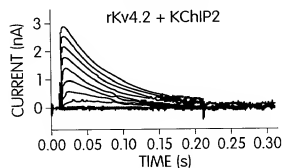
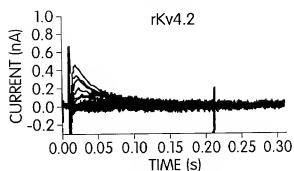
Monkey KChIP4d protein sequence

MNVRVVISIAQLEEASSSTGGFLYAQNSTKRSIKERIMKLLPCSAKTSPPAIQNSVEDELEMATVHRHPEALELLEAQS
KFTKKELQILYRGFKNECPSGVVNEETFEKIYSQFFPQGDSTTYAHFLNFAFTDTHNGAVSFEDFIKGLSILLRGTVQEK
LNWAFNLYDINKDGIYIKBEMLDIMKAIYDMMGKCTYPVLKEDAPRQHVETFFQKMDKNKDGVTITDEFIESCQKDENIM
RSMQLFENVI.

Fig. 36



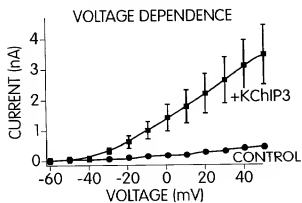
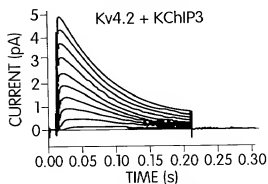
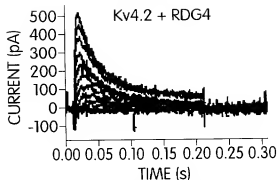
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CURRENT PARAMETER	CHO	
	rKv4.2	rKv4.2 + KChIP2
PEAK CURRENT (nA/cell, at 50 mV)	0.51 ±0.098	3.3 ±0.45
PEAK CURRENT DENSITY (pA/pF, at 50 mV)	18.6 ±2.8	196.6 ±26.6
INACTIVATION TIME CONSTANT (ms, at 50 mV)	28.47 ±3.5	95.14 ±8.3
RECOVERY FROM INACTIVATION TIME CONSTANT (ms, at -80 mV)	257.9	49.5
ACTIVATION $V_{1/2}$ (mV)	20.5	-2.2
STEADY-STATE INACTIVATION $V_{1/2}$ (mV)	-47.1	-45.7

Fig. 38

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CURRENT PARAMETER	CHO	
	rKv4.2 +RBG4	rKv4.2 +KChIP3
PEAK CURRENT (nA/cell, at 50 mV)	0.46 ±0.084	3.5 ±0.99
PEAK CURRENT DENSITY (pA/pF, at 50 mV)	29.7 ±11.2	161.7 ±21.8
INACTIVATION TIME CONSTANT (ms, at 50 mV)	29.5 ±9.5	67.2 ±14.1
RECOVERY FROM INACTIVATION TIME CONSTANT (ms, at -80 mV)	435.9	130.8
ACTIVATION $V_{1/2}$ (mV)	4.1	6.1

Fig. 39

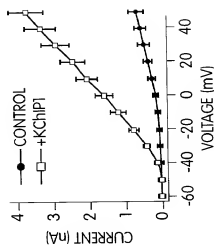


Fig. 40C

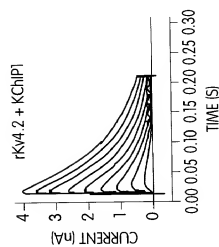


Fig. 40B

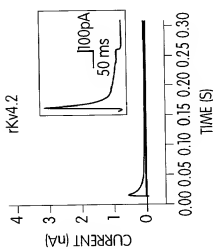


Fig. 40A

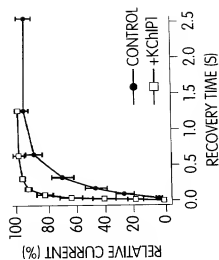


Fig. 40F

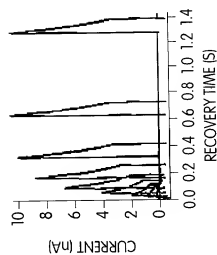


Fig. 40E

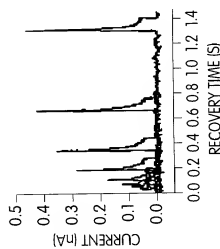


Fig. 40D

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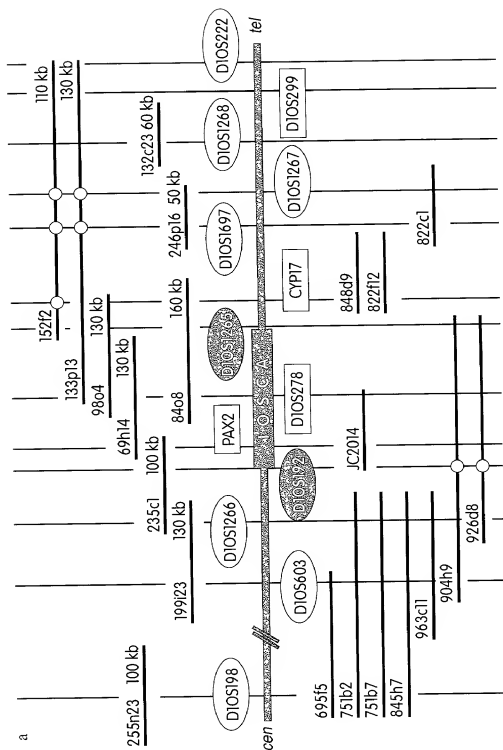


Fig. 42

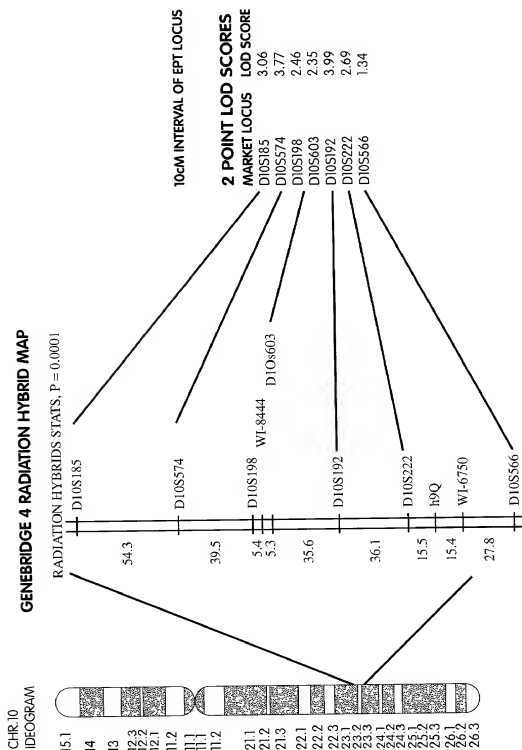


Fig. 43

Attorney's
Docket
Number MNI-070CP4

Declaration, Petition and Power of Attorney
for Continuation-in-Part Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

POTASSIUM CHANNEL INTERACTORS AND USES THEREFOR

the specification of which

(check one)

☐ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

This application in part discloses and claims subject matter disclosed in my earlier filed application(s), as follows:

- ☒ Serial No. 60/110,033, filed November 25, 1998 ;
Serial No. 60/109,333, filed November 20, 1998
Serial No. 60/110,277, filed November 30, 1998 , as to which I claim priority
benefit under Title 35, United States Code, §119(e).
- ☒ Serial No. 09/298,731 , filed April 23, 1999 ;
Serial No. 09/350,614 , filed July 9, 1999 ;
Serial No. 09/350,874 , filed July 9, 1999 ;
Serial No. 09/399,913 , filed September 21, 1999 ;
Serial No. 09/400,492 , filed September 21, 1999 , as to which I claim priority
benefit under Title 35, United States Code, §120.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56, including all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of the continuation-in-part application.

AS TO PARENT APPLICATION:

As to the subject matter of this application which is common to said earlier application, I do not know and do not believe that the same was ever known or used in the United States of America before my or our invention thereof or patented or described in any printed publication in any country before my or our invention thereof, or more than one year prior to said earlier application, or in public use or on sale in the United States of America more than one year prior to said earlier application; that the common subject matter has not been patented or made the subject of an inventor's certificate issued before the date of said earlier application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months prior to said earlier application; and

As to applications for patents or inventor's certificate or PCT international application(s) designating at least one country other than the United States of America, on the common subject matter, filed in or designating any country foreign to the United States of America, prior to said earlier application by me or my legal representatives or assigns,

Check one:

- ☒ no such applications have been filed.
☐ such applications have been filed as follows

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED WITHIN 12 MONTHS
 (6 MONTHS FOR DESIGN) PRIOR TO SAID EARLIER U.S. APPLICATION

Country	Application Number	Date of Filing (month,day,year)	Priority Claimed Under 35 USC 119
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No

ALL FOREIGN APPLICATION(S), IF ANY, FILED MORE THAN 12 MONTHS
 (6 MONTHS FOR DESIGN) PRIOR TO SAID EARLIER U.S. APPLICATION

09670756-092700
 007260-95207960

AS TO THIS APPLICATION:

As to the subject matter of this application which is not common to said earlier application, I do not know and do not believe that the same was ever known or used in the United States of America before my or our invention thereof or patented or described in any printed publication in any country before my or our invention thereof, or more than one year prior to this application, or in public use or on sale in the United States of America more than one year prior to this application; that said non-common subject matter has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months prior to this application; and

As to applications for patents or inventor's certificate or PCT international application(s) designating at least one country other than the United States of America, on said non-common subject matter, filed in or designating any country foreign to the United States of America, prior to this application by me or my legal representatives or assigns,

Check one:

☐ no such applications have been filed.

☒ such applications have been filed as follows

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED WITHIN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

Country	Application Number	Date of Filing (month,day,year)	Priority Claimed Under 35 USC 119
PCT	PCT/US99/27428	11/19/99	<input checked="" type="checkbox"/> Yes No <input type="checkbox"/>
			<input type="checkbox"/> Yes No <input type="checkbox"/>
			<input type="checkbox"/> Yes No <input type="checkbox"/>
			<input type="checkbox"/> Yes No <input type="checkbox"/>
			<input type="checkbox"/> Yes No <input type="checkbox"/>

ALL FOREIGN APPLICATION(S), IF ANY, FILED MORE THAN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

09670755.002710

CLAIM FOR BENEFIT OF U.S. PROVISIONAL APPLICATION(S)

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

<u>60/110,033</u>	<u>November 25, 1998</u>
(Application Serial No.)	(Filing Date)

<u>60/109,333</u>	<u>November 20, 1998</u>
(Application Serial No.)	(Filing Date)

<u>60/110,277</u>	<u>November 30, 1998</u>
(Application Serial No.)	(Filing Date)

CLAIM FOR BENEFIT OF U.S. PATENT APPLICATION(S)

I hereby claim the benefit under 35 U.S.C. §120 of any United States patent application(s) listed below.

<u>09/298,731</u>	<u>April 23, 1999</u>
(Application Serial No.)	(Filing Date)

<u>09/350,614</u>	<u>July 9, 1999</u>
(Application Serial No.)	(Filing Date)

<u>09/350,874</u>	<u>July 9, 1999</u>
(Application Serial No.)	(Filing Date)

<u>09/399,913</u>	<u>September 21, 1999</u>
(Application Serial No.)	(Filing Date)

<u>09/400,492</u>	<u>September 21, 1999</u>
(Application Serial No.)	(Filing Date)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

James E. Cockfield	Reg. No. 19,162	Nicholas P. Triano III	Reg. No. 36,397
Thomas V. Smurzynski	Reg. No. 24,798	Peter C. Lauro	Reg. No. 32,360
Ralph A. Loren	Reg. No. 29,325	DeAnn F. Smith	Reg. No. 36,683
Giulio A. DeConti, Jr.	Reg. No. 31,503	William D. DeVaul	Reg. No. 42,483
Ann Lamport Hammitte	Reg. No. 34,858	David J. Rikkers	Reg. No. 43,882
Elizabeth A. Hanley	Reg. No. 33,505	Chi Suk Kim	Reg. No. 42,728
Amy E. Mandragouras	Reg. No. 36,207	Maria C. Laccotripe	Limited Recognition
Anthony A. Laurentano	Reg. No. 38,220		Under 37 C.F.R. § 10.9(b)
Jane E. Remillard	Reg. No. 38,872	Debra J. Milasincic	Reg. No. P46,931
Jeremiah Lynch	Reg. No. 17,425	David R. Burns	Reg. No. P46,590
Kevin J. Canning	Reg. No. 35,470	Sean D. Detweiler	Reg. No. 42,482
Jeanne M. DiGiorgio	Reg. No. 41,710	Peter S. Stecher	Reg. No. P47,259
Megan E. Williams	Reg. No. 43,270		

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Wherefore I petition that letters patent be granted to me for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe my name to said specification and claims and to the foregoing declaration, power of attorney, and this petition.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Citizenship U.S.	
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Inventor's signature	Date
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Kenneth Rhodes *et al.*

Serial No.: N/A

Filed: Herewith

For: *POTASSIUM CHANNEL INTERACTORS AND
USES THEREFOR*

Attorney Docket No.: MNI-070CP4

Assistant Commissioner for Patents
Box Sequence
Washington, D.C. 20231

TRANSMITTAL LETTER FOR DISKETTE CONTAINING SEQUENCE LISTING

Dear Sir:

Enclosed is a diskette which contains a computer readable form of the Sequence Listing for the patent application filed herewith. The Sequence Listing complies with the requirements of 37 C.F.R. § 1.821. The material on this diskette is identical in substance to the sequence listing appearing on pages 1-92 of the Sequence Listing which is submitted herewith, as required by 37 C.F.R. § 1.821(f). The computer readable form of the Sequence Listing contained on the enclosed diskette is understood to comply with the requirements of § 1.824(d).

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Signature

Nelson F. Barros

Nelson F. Barros

Please Print Name of Person Signing

LAHIVE & COCKFIELD, LLP
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By

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An, Wengian

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ctttctacaa aacctggcac cgcgtggctc agtctctgat tgccaactct tctcctctcc 911

tctctcttgag agggacgagc tgaatatcca agtttgtttt ggaagcatgc ccactctctcc 971

atgctgtctgc tgccctgtgg aaggcccttc tgcttgagct taacacagtag tgcacagttt 1031

tctgogtata cagatcccca actcaactgcc tctaagtcag gcagaccctg atcaatctga 1091

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 tatccctctt ctccatcccc tgcacaagcc cagcactgca tgtctctccc ggaaggtcca 1451
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 <212> PRT
 <213> Rattus sp.

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 20 25 30
 Lys Ile Glu Asp Asp Leu Glu Met Thr Met Val Cys His Arg Pro Glu
 35 40 45
 Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr Lys Arg Glu Leu
 50 55 60
 Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val Val
 65 70 75 80
 Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln Phe Phe Pro His Gly
 85 90 95
 Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala Phe Asp Thr Thr
 100 105 110
 Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr Ala Leu Ser Ile
 115 120 125
 Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp Thr Phe Asn Leu
 130 135 140
 Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu Glu Met Met Asp
 145 150 155 160
 Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Val
 165 170 175
 Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val Phe Phe Gln Lys
 180 185 190
 Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp Glu Phe Leu Glu

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acc tat cct gtg ctc aaa gag gac act ccc agg cag cat gtg gat gtc	640	
Thr Tyr Pro Val Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val	175 180 185	
ttc ttc cag aaa atg gat aaa aat aaa gat gcc att gta acg tta gat	688	
Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp	190 195 200	
gaa ttt ctt gaa tca tgt cag gag gat gac aac atc atg aga tct cta	736	
Glu Phe Leu Glu Ser Cys Gln Glu Asp Asp Asn Ile Met Arg Ser Leu	205 210 215 220	
cag ctg ttc caa aat gtc atg taactgagga cactggccat tctgctctca	787	
Gln Leu Phe Gln Asn Val Met	225	
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<222> (345) .. (953)
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sequence may be any amino acid

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gaaaacgggg aaataaaaagc aaagattacc atgaattgca agattaccta gcaattgcaa 180
ggtaggagga gagaggtgga ggcgcgaqta gacaggaggq agggagaaaq tgaagqaaag 240
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					Met Leu Thr Gln	
					1	
ggc gag tct gaa ggg ctc cag acc ttg ggg ata gta gtg gtc ctg tgt	404					
Gly Glu Ser Glu Gly Leu Gln Thr Leu Gly Ile Val Val Val Val Leu Cys						
5 10 15 20						
tcc tct ctg aaa cta ctg cac tac ctc ggg ctg att gac ttg tgg gat	452					
Ser Ser Leu Lys Leu Leu His Tyr Leu Leu Ile Asp Leu Ser Asp						
25 30 35						
gac aag atc gag gat gat ctg gag atg acc atg gtt tgc cat cgg cct	500					
Asp Lys Ile Glu Asp Asp Leu Glu Met Thr Met Val Cys His Arg Pro						
40 45 50						
gag gga ctg gag cag ctt gag gca cag acg aac ttc acc aag aga gaa	548					
Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr Lys Arg Glu						
55 60 65						
ctg caa gtc ctt tac cgg gga ttc aaa aac gag tgc ccc agt ggt gtg	596					
Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val						
70 75 80						
gtt aac gaa gag aca ttc aag cng atc tac gct cag ttt ttc cct cat	644					
Val Asn Glu Glu Thr Phe Lys Xaa Ile Tyr Ala Gln Phe Phe Pro His						
85 90 95 100						
gga gat gcc agc aca tac gca cat tac ctc ttc aat gcc ttc gac acc	692					
Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala Phe Asp Thr						
105 110 115						
acc cag aca ggc tct gta aag ttc gag gac ttt gtg act gct ctg tgg	740					
Thr Gln Thr Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr Ala Leu Ser						
120 125 130						
att tta ctg aga gga acg gtc cat gaa aaa ctg aag tgg acg ttt aat	788					
Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Lys Trp Thr Phe Asn						
135 140 145						
ttg tac gac atc aaa gac ggc tac ata aac aaa gag gag atg atg	836					
Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu Glu Met Met						
150 155 160						
gac ata gtg aaa gcc atc tat gac atg atg ggg aaa tac acc tat ctt	884					
Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Leu						
165 170 175 180						
gtg ctc aaa gag gac act tcc agg cag cac gtg gac gtc ttc ttc cag	932					
Val Leu Lys Glu Asp Thr Ser Arg Gln His Val Asp Val Phe Phe Gln						
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<213> Rattus sp.
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Val	Val	Leu	Cys	Ser	Ser	Leu	Lys	Leu	Leu	His	Tyr	Leu	Gly	Leu	Ile
			20					25					30		
Asp	Leu	Ser	Asp	Asp	Lys	Ile	Glu	Asp	Asp	Leu	Glu	Met	Thr	Met	Val
		35					40					45			
Cys	His	Arg	Pro	Glu	Gly	Leu	Glu	Gln	Leu	Glu	Ala	Gln	Thr	Asn	Phe
	50					55					60				
Thr	Lys	Arg	Glu	Leu	Gln	Val	Leu	Tyr	Arg	Gly	Phe	Lys	Asn	Glu	Cys
	65				70					75					80
Pro	Ser	Gly	Val	Val	Asn	Glu	Glu	Thr	Phe	Lys	Xaa	Ile	Tyr	Ala	Gln
				85					90					95	
Phe	Phe	Pro	His	Gly	Asp	Ala	Ser	Thr	Tyr	Ala	His	Tyr	Leu	Phe	Asn
			100					105					110		
Ala	Phe	Asp	Thr	Thr	Gln	Thr	Gly	Ser	Val	Lys	Phe	Glu	Asp	Phe	Val
		115					120					125			
Thr	Ala	Leu	Ser	Ile	Leu	Leu	Arg	Gly	Thr	Val	His	Glu	Lys	Leu	Lys
	130					135					140				
Trp	Thr	Phe	Asn	Leu	Tyr	Asp	Ile	Asn	Lys	Asp	Gly	Tyr	Ile	Asn	Lys
145				150						155				160	
Glu	Glu	Met	Met	Asp	Ile	Val	Lys	Ala	Ile	Tyr	Asp	Met	Met	Gly	Lys
				165					170					175	
Tyr	Thr	Tyr	Leu	Val	Leu	Lys	Glu	Asp	Thr	Ser	Arg	Gln	His	Val	Asp
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<212> DNA
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ccgccagggg gcacgtgtg agcgccttat ccgggccacc cggcgccccc tcccagacc 180

cgggcgaggag	cggggcgccg	ggggccc	atg	cgg	ggc	cag	ggc	cgc	aag	gag	agt		233			
			Met	Arg	Gly	Gln	Gly	Arg	Lys	Glu	Ser					
				1				5								
ttg	tcc	gat	tcc	cga	gac	ctg	gac	ggc	tcc	tac	gac	cag	ctc	acg	ggc	281
Leu	Ser	Asp	Ser	Arg	Asp	Leu	Asp	Gly	Ser	Tyr	Asp	Gln	Leu	Thr	Gly	
	10				15					20					25	
cac	cct	cca	ggg	ccc	act	aaa	aaa	gcg	ctg	aag	cag	cga	ttc	ctc	aag	329
His	Pro	Pro	Gly	Pro	Thr	Lys	Lys	Ala	Leu	Lys	Gln	Arg	Phe	Leu	Lys	
				30					35					40		
ctg	ctg	cgg	tgc	tgc	ggg	ccc	caa	ggc	ctg	ccc	tca	gtc	agt	gaa	aca	377
Leu	Leu	Pro	Cys	Cys	Gly	Pro	Gln	Ala	Leu	Pro	Ser	Val	Ser	Glu	Thr	
			45					50					55			
tta	gcc	gcc	cca	gcc	tcc	ctc	cgc	ccc	cac	aga	ccc	cgc	ctg	ctg	gac	425
Leu	Ala	Ala	Pro	Ala	Ser	Leu	Arg	Pro	His	Arg	Pro	Arg	Leu	Leu	Asp	
		60					65					70				
cca	gac	agc	gtg	gac	gat	gaa	ttt	gaa	ttg	tcc	acc	gtg	tgt	cac	cgg	473
Pro	Asp	Ser	Val	Asp	Asp	Glu	Phe	Glu	Leu	Ser	Thr	Val	Cys	His	Arg	
		75				80					85					
cct	gag	ggc	ctg	gag	cag	ctg	cag	gag	caa	acc	aaa	ttc	acg	cgc	aag	521
Pro	Glu	Gly	Leu	Glu	Gln	Leu	Gln	Glu	Gln	Thr	Lys	Phe	Thr	Arg	Lys	
	90				95					100					105	
gag	ttg	cag	gtc	ctg	tac	cgg	ggc	ttc	aag	aac	gaa	tgt	ccc	agc	gga	569
Glu	Leu	Gln	Val	Leu	Tyr	Arg	Gly	Phe	Lys	Asn	Glu	Cys	Pro	Ser	Gly	
			110						115					120		
att	gtc	aat	gag	gag	aac	ttc	aag	cag	att	tac	tcc	cag	ttc	ttt	cct	617
Ile	Val	Asn	Glu	Glu	Asn	Phe	Lys	Gln	Ile	Tyr	Ser	Gln	Phe	Phe	Pro	
			125					130					135			
caa	gga	gac	tcc	agc	acc	tat	gcc	act	ttt	ctc	ttc	aat	gcc	ttt	gac	665
Gln	Gly	Asp	Ser	Ser	Thr	Tyr	Ala	Thr	Phe	Leu	Phe	Asn	Ala	Phe	Asp	
		140					145					150				
acc	aac	cat	gat	ggc	tgc	gtc	agt	ttt	gag	gac	ttt	gtg	gct	ggc	ttg	713
Thr	Asn	His	Asp	Gly	Ser	Val	Ser	Phe	Glu	Asp	Phe	Val	Ala	Gly	Leu	
		155				160				165						
tcc	gtg	att	ctt	cgg	gga	act	gta	gat	gac	agg	ctt	aat	tgg	gcc	ttc	761
Ser	Val	Ile	Leu	Arg	Gly	Thr	Val	Asp	Asp	Arg	Leu	Asn	Trp	Ala	Phe	
	170				175					180				185		
aac	ctg	tat	gac	ctt	aac	aag	gac	ggc	tgc	atc	acc	aag	gag	gaa	atg	809
Asn	Leu	Tyr	Asp	Leu	Asn	Lys	Asp	Gly	Cys	Ile	Thr	Lys	Glu	Glu	Met	
				190					195					200		
ctt	gac	atc	atg	aag	tcc	atc	tat	gac	atg	atg	ggc	aag	tac	acg	tac	857
Leu	Asp	Ile	Met	Lys	Ser</											

	220		225		230	
cag aag atg gac aga aac aag gat ggt gtg gtg acc att gag gaa ttc						953
Gln Lys Met Asp Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe						
235		240		245		
att gag tct tgt caa aag gat gag aac atc atg agg tcc atg cag ctg						1001
Ile Glu Ser Cys Gln Lys Asp Glu Asn Ile Met Arg Ser Met Gln Leu						
250		255		260	265	
ttt gac aat gtc atc tagccccag gagagggggt cagtgtttcc tggggggacc						1056
Phe Asp Asn Val Ile	270					
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acgcctccct gggggctgga gggatccaag agcttgggga ttcagtagtc cagatctctg						1176
gagctgaagg ggccagagag tgggcagagt gcactctoggg ggggtgttccc aactcccacc						1236
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<213> Homo sapiens						
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20 25 30						
Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro						
35 40 45						

Gln Ala Leu Pro Ser Val Ser Glu Thr Leu Ala Ala Pro Ala Ser Leu
50 55 60

Arg Pro His Arg Pro Arg Leu Leu Asp Pro Asp Ser Val Asp Asp Glu
65 70 75 80

Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu
85 90 95

Gln Glu Gln Thr Lys Phe Thr Arg Lys Glu Leu Gln Val Leu Tyr Arg
100 105 110

Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe
115 120 125

Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr Tyr
130 135 140

Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val
145 150 155 160

Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr
165 170 175

Val Asp Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys
180 185 190

Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile
195 200 205

Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala
210 215 220

Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys
225 230 235 240

Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Lys Asp
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Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val Ile
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<211> 1247

<212> DNA

<213> Rattus sp.

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<221> CDS

<222> (2)..(772)

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ccc agt aaa aaa gcc ctg aag cag cgt ttc ctc aag ctg ctg ccg tgc 97
Pro Ser Lys Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys

002601 952266

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acaaaagtag	gcaagagtag	gcaagctaaa	tctgggggct	tcccaacccc	cgacagctct	1002
cacccctctt	caactgatac	ctagtgtgtg	ggacacccct	ggtgtaggga	ccaagtgggt	1062
ctccaccttc	tagtcccact	ctagaaacca	cattagacag	aaggtctcct	gctatgggtc	1122
tttccccttc	cctaattctt	tagattttcc	tcaagactcc	cttctcagag	aacacgtctt	1182
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<211> 257
<212> PRT
<213> Rattus sp.
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Pro	Ser	Lys	Lys	Ala	Leu	Lys	Gln	Arg	Phe	Leu	Lys	Leu	Leu	Pro	Cys	
			20					25						30		
Cys	Gly	Pro	Gln	Ala	Leu	Pro	Ser	Val	Ser	Glu	Thr	Leu	Ala	Ala	Pro	
		35					40					45				
Ala	Ser	Leu	Arg	Pro	His	Arg	Pro	Arg	Pro	Leu	Asp	Pro	Asp	Ser	Val	
		50				55					60					
Glu	Asp	Glu	Phe	Glu	Leu	Ser	Thr	Val	Cys	His	Arg	Pro	Glu	Gly	Leu	
					70					75					80	
Glu	Gln	Leu	Gln	Glu	Gln	Thr	Lys	Phe	Thr	Arg	Arg	Glu	Leu	Gln	Val	
				85					90					95		
Leu	Tyr	Arg	Gly	Phe	Lys	Asn	Glu	Cys	Pro	Ser	Gly	Ile	Val	Asn	Glu	
			100					105					110			
Glu	Asn	Phe	Lys	Gln	Ile	Tyr	Ser	Gln	Phe	Phe	Pro	Gln	Gly	Asp	Ser	
			115				120					125				
Ser	Asn	Tyr	Ala	Thr	Phe	Leu	Phe	Asn	Ala	Phe	Asp	Thr	Asn	His	Asp	
		130				135					140					
Gly	Ser	Val	Ser	Phe	Glu	Asp	Phe	Val	Ala	Gly	Leu	Ser	Val	Ile	Leu	
					150					155					160	
Arg	Gly	Thr	Ile	Asp	Asp	Arg	Leu	Ser	Trp	Ala	Phe	Asn	Leu	Tyr	Asp	
				165					170					175		
Leu	Asn	Lys	Asp	Gly	Cys	Ile	Thr	Lys	Glu	Glu	Met	Leu	Asp	Ile	Met	
			180					185					190			
Lys	Ser	Ile	Tyr	Asp	Met	Met	Gly	Lys	Tyr	Thr	Tyr	Pro	Ala	Leu	Arg	

195 200 205

Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp
210 215 220

Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys
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Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val
245 250 255

Ile

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<211> 2343
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (181)..(990)

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ctatctctggc cacccgggcgc cccctccac ggcccaggcg ggagcggggc gccggggggcc 180
atg cgg ggc caa ggc cga aag gag agt ttg tcc gaa tcc cga gat ttg 228
Met Arg Gly Gln Gly Arg Lys Glu Ser Leu Ser Glu Ser Arg Asp Leu
1 5 10 15
gac ggc tcc tat gac cag ctt acg ggc cac cct cca ggg ccc agt aaa 276
Asp Gly Ser Tyr Asp Gln Leu Thr Gly His Pro Pro Gly Pro Ser Lys
20 25 30
aaa gcc ctg aag cag cgt ttc ctc aag ctg ctg ccg tgc tgc ggg ccc 324
Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro
35 40 45
caa gcc ctg ccc tca gtc agt gaa aca tta gct gcc cca gcc tcc ctc 372
Gln Ala Leu Pro Ser Val Ser Glu Thr Leu Ala Ala Pro Ala Ser Leu
50 55 60
cgc ccc cac aga ccc cgc ccg ctg gac cca gac agc gtg gag gat gag 420
Arg Pro His Arg Pro Arg Pro Leu Asp Pro Asp Ser Val Glu Asp Glu
65 70 75 80
ttt gaa cta tcc acg gtg tgc cac cgg cct gag ggt ctg gaa caa ctc 468
Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu
85 90 95
cag gaa caa acc aag ttc aca cgc aga gag ttg cag gtc ctg tac aga 516
Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg
100 105 110
ggc ttc aag aac gaa tgt ccc agc gga att gtc aac gag gag aac ttc 564
Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe

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Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro
 35 40 45

Gln Ala Leu Pro Ser Val Ser Glu Thr Leu Ala Ala Pro Ala Ser Leu
 50 55 60

Arg Pro His Arg Pro Arg Pro Leu Asp Pro Asp Ser Val Glu Asp Glu
 65 70 75 80

Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Lys Leu
 85 90 95

Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg
 100 105 110

Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe
 115 120 125

Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Asn Tyr
 130 135 140

Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val
 145 150 155 160

Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr

165 170 175

Ile Asp Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys
180 185 190

Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile
195 200 205

Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala
210 215 220

Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys
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cgggcgagg cgggcgccg ggggcc atg cgg ggc cag ggc cgc aag gag agt 233
Met Arg Gly Gln Gly Arg Lys Glu Ser
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ttg tcc gat tcc cga gac ctg gac ggc tcc tac gac cag ctc acg ggc 281
Leu Ser Asp Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Gly
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cac cct cca ggg ccc act aaa aaa gcg ctg aag cag cga ttc ctc aag 329
His Pro Pro Gly Pro Thr Lys Lys Ala Leu Lys Gln Arg Phe Leu Lys
30 35 40
ctg ctg ccg tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aac 377
Leu Leu Pro Cys Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Asn
45 50 55
agc gtg gac gat gaa ttt gaa ttg tcc acc gtg tgt cac cgg cct gag 425
Ser Val Asp Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu
60 65 70
ggt ctg gag cag ctg cag gag caa acc aaa ttc acg cgc aag gag ttg 473
Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Lys Glu Leu
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aat gag gag aac ttc aag cag att tac tcc cag ttc ttt cct caa gga 569
 Asn Glu Glu Asn Phe Lys Gln Ile Tyr tcc Gln Phe Phe Pro Gln Gly 120
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gac tcc agc acc tat gcc act ttt ctc ttc aat gcc ttt gac acc aac 617
 Asp Ser Ser Thr Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn 135
 125 130

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 His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val 150
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tat gac ctt aac aag gac ggc tgc atc acc aag gag gaa atg ctt gac 761
 Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp 185
 170 175 180

atc atg aag tcc atc tat gac atg atg ggc aag tac acg tac cct gca 809
 Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala 200
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ctc cgg gag gag gcc cca agg gaa cac gtg gag agc ttc ttc cag aag 857
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atg gac aga aac aag gat ggt gtg gtg acc att gag gaa ttc att gag 905
 Met Asp Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu 230
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tct tgt caa aag gat gag aac atc atg agg tcc atg cag ctc ttt gac 953
 Ser Cys Gln Lys Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp 245
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aat gtc atc tagccccag gagaggggt cagtgtttcc tggggggacc 1002
 Asn Val Ile 250

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<212> PRT

<213> Homo sapiens

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Lys	Ala	Leu	Lys	Gln	Arg	Phe	Leu	Lys	Leu	Leu	Pro	Cys	Cys	Gly	Pro
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Gln	Ala	Leu	Pro	Ser	Val	Ser	Glu	Asn	Ser	Val	Asp	Asp	Glu	Phe	Glu
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Leu	Ser	Thr	Val	Cys	His	Arg	Pro	Glu	Gly	Leu	Glu	Gln	Leu	Gln	Glu
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Gln	Thr	Lys	Phe	Thr	Arg	Lys	Glu	Leu	Gln	Val	Leu	Tyr	Arg	Gly	Phe
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Lys	Asn	Glu	Cys	Pro	Ser	Gly	Ile	Val	Asn	Glu	Glu	Asn	Phe	Lys	Gln
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Ile	Tyr	Ser	Gln	Phe	Phe	Pro	Gln	Gly	Asp	Ser	Ser	Thr	Tyr	Ala	Thr
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Phe	Leu	Phe	Asn	Ala	Phe	Asp	Thr	Asn	His	Asp	Gly	Ser	Val	Ser	Phe
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Glu	Asp	Phe	Val	Ala	Gly	Leu	Ser	Val	Ile	Leu	Arg	Gly	Thr	Val	Asp
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Asp	Arg	Leu	Asn	Trp	Ala	Phe	Asn	Leu	Tyr	Asp	Leu	Asn	Lys	Asp	Gly
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Cys	Ile	Thr	Lys	Glu	Glu	Met	Leu	Asp	Ile	Met	Lys	Ser	Ile	Tyr	Asp
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Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala Pro Arg
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Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
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cacggcccag gcgggagcgg ggcgcgggg gcc atg cgg gcc caa gcc aga aag 234
Met Arg Gly Gln Gly Arg Lys
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gag agt ttg tcc gaa tcc cga gat ctg gac gcc tcc tat gac cag ctt 282
Glu Ser Leu Ser Glu Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu
10 15 20

acg gcc cac cct cca ggg ccc agt aaa aaa gcc ctg aag cag cgt ttc 330
Thr Gly His Pro Pro Gly Pro Ser Lys Lys Ala Leu Lys Gln Arg Phe
25 30 35

ctc aag ctg ctg cgg tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt 378
Leu Lys Leu Leu Pro Cys Cys Gly Pro Gln Ala Leu Pro Ser Val Ser
40 45 50 55

gaa aac agc gta gag gat gag ttt gaa tta tcc acg gtg tgt cac cga 426
Glu Asn Ser Val Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg
60 65 70

cct gag ggc ctg gaa caa ctc cag gaa cag acc aag ttc aca cgc aga 474
Pro Glu Gly Leu Glu Gln Leu Gln Glu Thr Lys Phe Thr Arg Arg
75 80 85

gag ctg cag gtc ctg tac cga gcc ttc aag aac gaa tgc ccc agt ggg 522
Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly
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Ile Val Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro
105 110 115

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acc aac cac gat ggc tct gtc agt ttt gag gac ttt gtg gct ggt ttg 666
 Thr Asn His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu
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tcg gtg att ctt cgg ggg acc ata gat gat aga ctg agc tgg gct ttc 714
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 155 160 165

aac tta tat gac ctc aac aag gac ggc tgt atc aca aag gag gaa atg 762
 Asn Leu Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met
 170 175 180

ctt gac att atg aag tcc atc tat gac atg atg ggc aag tac aca tac 810
 Leu Asp Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr
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cct gcc ctc cgg gag gag gcc cca aga gaa cac gtg gag agc ttc ttc 858
 Pro Ala Leu Arg Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe
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cag aag atg gac agg aac aag gac ggc gtg gtg acc atc gag gaa ttc 906
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atc gag tct tgt caa cag gac gag aac atc atg agg tcc atg cag ctc 954
 Ile Glu Ser Cys Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu
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 Phe Asp Asn Val Ile
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 35 40 45
 Gln Ala Leu Pro Ser Val Ser Glu Asn Ser Val Glu Asp Glu Phe Glu
 50 55 60
 Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
 65 70 75 80
 Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe
 85 90 95
 Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
 100 105 110
 Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Asn Tyr Ala Thr
 115 120 125
 Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
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 Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Ile Asp
 145 150 155 160
 Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
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 Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp

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Val	Val	Thr	Ile	Glu	Glu	Phe	Ile	Glu	Ser	Cys	Gln	Gln	Asp	Glu	Asn						
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Ile	Met	Arg	Ser	Met	Gln	Leu	Phe	Asp	Asn	Val	Ile										
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Asn Val Ile			
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 Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
 35 40 45
 Gln Thr Lys Phe Thr Arg Lys Glu Leu Gln Val Leu Tyr Arg Gly Phe
 50 55 60
 Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
 65 70 75 80
 Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr Tyr Ala Thr
 85 90 95
 Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
 100 105 110
 Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Val Asp
 115 120 125
 Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
 130 135 140
 Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
 145 150 155 160
 Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala Pro Arg
 165 170 175
 Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
 180 185 190
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 Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val Ile
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 <213> Simian sp.

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 <400> 25

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 1 5 10
 Met Arg Gly Gln Gly Arg Lys Glu Ser Leu Ser Asp Ser
 cga gac ctg gac gga tcc tac gac cag ctc acg gac agc gtg gag gat 219
 Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Asp Ser Val Glu Asp
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 gaa ttt gaa ttg tcc acc gtg tgt cac cgg cct gag ggt ctg gag cag 267
 Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln
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 ctg cag gag caa acc aaa ttc acg cgc aag gag ttg cag gtc ctg tac 315
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 cgg ggc ttc aag aac gaa tgt ccg agc gga att gtc aat gag gag aac 363
 Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn
 65 70 75
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 Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr
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 Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser
 95 100 105
 gtc agt ttt gag gac ttt gtg gct ggt ttg tcc gtg att ctt cgg gga 507
 Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly
 110 115 120 125
 act gta gat gac agg ctt aat tgg gcc ttc aac ttg tat gac ctc aac 555
 Thr Val Asp Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn
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 aag gac ggc tgc atc acc aag gag gaa atg ctt gac atc atg aag tcc 603
 Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser
 145 150 155
 atc tat gac atg atg ggc aag tac aca tac cct gca ctc cgg gag gag 651
 Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu
 160 165 170
 gcc cca agg gaa cat gtg gag aac ttc ttc cag aag atg gac aga aac 699
 Ala Pro Arg Glu His Val Glu Asn Phe Phe Gln Lys Met Asp Arg Asn
 175 180 185
 aag gat ggc gtg gtg acc att gag gaa ttc att gag tct tgt caa aag 747
 Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Lys
 190 195 200 205
 gat gag aac atc atg agg tcc atg cag ctc ttt gac aat gtc atc 792
 Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val Ile
 210 215 220

00260-92700

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<211> 220

<212> PRT

<213> Simian sp.

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	20							25					30		

09670756.096700

09670756, 09670700

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 Leu Ser Glu Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Gly
 10 15 20 25

cac cct cca ggg ccc agt aaa aaa gcc ctg aag cag cgt ttc ctc aag 330
 His Pro Pro Gly Pro Ser Lys Lys Ala Leu Lys 35 40
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ctg ctg ccg tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aac 378
 Leu Leu Pro Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Asn 55
 45 50

agc gta gag gat gag ttt gaa tta tcc acg gtg tgt cac cga cct gag 426
 Ser Val Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu 70
 60 65

ggc ctg gaa caa ctc cag gaa cag acc aag ttc aca cgc aga gag ctg 474
 Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu 85
 75 80

cag gtc ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg att gtc 522
 Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val 105
 90 95 100

aac gag gag aac ttc aag cag att tat tct cag ttc ttt ccc caa gga 570
 Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly 120
 110 115

gac tcc agc aac tat gct act ttt ctc ttc aat gcc ttt gac acc aac 618
 Asp Ser Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn 135
 125 130

cac gat ggc tct gtc agt ttt gag gac ttt gtg gct ggt ttg tgc gtg 666
 His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Glu Leu Ser Val 150
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att ctt cgg ggg acc ata gat gat aga ctg agc tgg gct ttc aac tta 714
 Ile Leu Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu 165
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tat gac ctc aac aag gac ggc tgt atc aca aag gag gaa atg ctt gac 762
 Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp 185
 170 175 180

att atg aag tcc atc tat gac atg atg ggc aag tac aca tac cct gcc 810
 Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala 200
 190 195

ctc cgg gag gag gcc cca aga gaa cac gtg gag agc ttc ttc cag aag 858
 Leu Arg Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys 215
 205 210

atg gac agg aac aag gac ggc gtg gtg acc atc gag gaa ttc atc gag 906
 Met Asp Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu 230
 220 225

tct tgt caa cag gac gag aac atc atg agg tcc atg cag ctc tca ccc 954
 Ser Cys Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu Ser Pro 245
 235 240

ctt ctc aac tgatacctag tgctgaggac acccctggtg tagggaccaa 1003
 Leu Leu Asn 250

03670756-002700

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<400> 28
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 Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro
 35 40 45
 Gln Ala Leu Pro Ser Val Ser Glu Asn Ser Val Glu Asp Glu Phe Glu
 50 55 60
 Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
 65 70 75 80
 Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe
 85 90 95

09670756-092700

Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
100 105 110

Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Asn Tyr Ala Thr
115 120 125

Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
130 135 140

Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Ile Asp
145 150 155 160

Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
165 170 175

Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
180 185 190

Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala Pro Arg
195 200 205

Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
210 215 220

Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Gln Asp Glu Asn
225 230 235 240

Ile Met Arg Ser Met Gln Leu Ser Pro Leu Leu Asn
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<210> 29

<211> 1904

<212> DNA

<213> Rattus sp.

<220>

<221> CDS

<222> (1) .. (675)

<400> 29

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cga tct ctc tac cag ttg gta act ggg tcg ctg tcg cca gac agc gta 96
Arg Ser Leu Tyr Gln Leu Val Thr Gly Ser Leu Ser Pro Asp Ser Val
20 25 30

gag gat gag ttt gaa tta tcc acg gtg tgt cac cga cct gag ggc ctg 144
Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu
35 40 45

gaa caa ctc cag gaa cag acc aag ttc aca cgc aga gag ctg cag gtc 192
Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val
50 55 60

ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg att gtc aac gag 240
Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu
65 70 75 80

256705, 052700

caatgtccca gaaattcacc atacacttct cagtgtcccg gatgatgcct gtcaaggtcc 1385
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<210> 30
 <211> 225
 <212> PRT
 <213> Rattus sp.

<400> 30
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 Arg Ser Leu Tyr Gln Leu Val Thr Gly Ser Leu Ser Pro Asp Ser Val
 20 25 30
 Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu
 35 40 45
 Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val
 50 55 60
 Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu
 65 70 75 80
 Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser
 85 90 95
 Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp
 100 105 110
 Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu
 115 120 125
 Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp
 130 135 140
 Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met
 145 150 155 160
 Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg
 165 170 175
 Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp

0067056.002700

ggc aca gtc cac gag aag ctc aag tgg gcc ttt aat ctc tac gac att 528
 Gly Thr Val His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile
 165 170 175

aac aag gat ggc tac atc acc aaa gag gag atg ctg gcc atc atg aag 576
 Asn Lys Asp Gly Tyr Ile Thr Lys Glu Met Leu Ala Ile Met Lys
 180 185 190

tcc atc tat gac atg atg ggc cgc cac acc tac ccc atc ctg cgg gag 624
 Ser Ile Tyr Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu
 195 200 205

gac gcg ccg gcg gag cac gtg gag agg ttc ttc gag aaa atg gac cgg 672
 Asp Ala Pro Ala Glu His Val Glu Arg Phe Phe Glu Lys Met Asp Arg
 210 215 220

aac cag gat ggg gta gtg acc att gaa gag ttc ctg gag gcc tgt cag 720
 Asn Gln Asp Gly Val Val Thr Ile Glu Glu Phe Leu Glu Ala Cys Gln
 225 230 235

aag gat gag aac atc atg agc tcc atg cag ctg ttt gag aat gtc atc 768
 Lys Asp Glu Asn Ile Met Ser Ser Met Gln Leu Phe Glu Asn Val Ile
 245 250 255

taggacacgt ccaaaggagt gcatggccac agccacctcc acccccaaga aacctccatc 828

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gctacacaca cacacacaca cacacacaca cacacacaca cacagccatt catctgggct 948

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 aaaaaaaaa aattcctgcg gccgcgttct cca 2841

<210> 32

<211> 256

<212> PRT

<213> Homo sapiens

<400> 32

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Gly Asp Leu Gly His Thr Pro Leu Ser Lys Lys Glu Gly Ile Lys Trp
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Gln Arg Pro Arg Leu Ser Arg Gln Ala Leu Met Arg Cys Leu Val
 35 40 45

Lys Trp Ile Leu Ser Ser Thr Ala Pro Gln Gly Ser Asp Ser Ser Asp
 50 55 60

Ser Glu Leu Glu Leu Ser Thr Val Arg His Gln Pro Glu Gly Leu Asp
 65 70 75 80

Gln Leu Gln Ala Gln Thr Lys Phe Thr Lys Lys Glu Leu Gln Ser Leu
 85 90 95

Tyr Arg Gly Phe Lys Asn Glu Cys Pro Thr Gly Leu Val Asp Glu Asp
 100 105 110

Thr Phe Lys Leu Ile Tyr Ala Gln Phe Phe Pro Gln Gly Asp Ala Thr
 115 120 125

Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Ala Asp Gly Asn Gly
 130 135 140

Ala Ile His Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg
 145 150 155 160

Gly Thr Val His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile
 165 170 175

Asn Lys Asp Gly Tyr Ile Thr Lys Glu Met Leu Ala Ile Met Lys
 180 185 190

Ser Ile Tyr Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu
 195 200 205

Asp Ala Pro Ala Glu His Val Glu Arg Phe Phe Glu Lys Met Asp Arg
 210 215 220

Asn Gln Asp Gly Val Val Thr Ile Glu Glu Phe Leu Glu Ala Cys Gln
 225 230 235 240

Lys Asp Glu Asn Ile Met Ser Ser Met Gln Leu Phe Glu Asn Val Ile
 245 250 255

<210> 33
 <211> 442
 <212> DNA
 <213> Rattus sp.

<220>
 <221> CDS
 <222> (1)..(327)

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 His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp
 20 25 30

ggt tac atc acc aaa gag gag atg ctg gcc atc atg aag tcc atc tac 144
 Gly Tyr Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys Ser Ile Tyr
 35 40 45

gac atg atg ggc cgc cac acc tac cct atc ctg cgg gag gac gca cct 192
 Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu Asp Ala Pro
 50 55 60

ctg gag cat gtg gag agg ttc ttc cag aaa atg gac agg aac cag gat 240
 Leu Glu His Val Glu Arg Phe Phe Gln Lys Met Asp Arg Asn Gln Asp
 65 70 75 80

gga gta gtg act att gat gaa ttt ctg gag act tgt cag aag gac gag 288

cgg ttc acc cgc cag gcc ctg atg cgt tgc tgc tta atc aag tgg atc 201
 Arg Phe Thr Arg Gln Ala Leu Met Arg Cys Cys Leu Ile Lys Trp Ile
 40 45 50

ctg tcc agt gct gcc cca caa ggc tca gac agc agt gac agt gaa ctg 249
 Leu Ser Ser Ala Ala Pro Gln Gly Ser Asp Ser Ser Asp Ser Glu Leu
 55 60 65

gag tta tcc acg gtg cgc cat cag cca gag gcc ttg gac cag cta caa 297
 Glu Leu Ser Thr Val Arg His Gln Pro Glu Gly Leu Asp Gln Leu Gln
 70 75 80

gct cag acc aag ttc acc aag aag gag ctg cag tcc ctt tac cga ggc 345
 Ala Gln Thr Lys Phe Thr Lys Lys Glu Leu Gln Ser Leu Tyr Arg Gly
 85 90 95

ttc aag aat gag tgt ccc aca ggc ctg gtg gat gaa gac acc ttc aaa 393
 Phe Lys Asn Glu Cys Pro Thr Gly Leu Val Asp Glu Asp Thr Phe Lys
 100 105 110 115

ctg att tat tcc cag ttc ttc cct cag gat gcc acc acc tat gca 441
 Leu Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ala Thr Thr Tyr Ala
 120 125 130

cac ttc ctg ttc aat gcc ttt gat gct gat ggg aac ggg gcc atc cac 489
 His Phe Leu Phe Asn Ala Phe Asp Ala Asp Gly Asn Gly Ala Ile His
 135 140 145

ttt gag gac ttt gtg gtt ggg ctg tcc atc ctg ctt cga ggg acg gtc 537
 Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg Gly Thr Val
 150 155 160

cat gag aag ctg aag tgg gcc ttc aat ctg tat gac att aac aag gat 585
 His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp
 165 170 175

ggt tgc atc acc aag gag gag atg ctg gcc atc atg aag tcc atc tac 633
 Gly Cys Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys Ser Ile Tyr
 180 185 190 195

gac atg atg ggc cgc cac acc tac ccc atc ctg cgg gag gat gca ccc 681
 Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu Asp Ala Pro
 200 205 210

ctg gag cat gtg gag agg ttc ttt cag aaa atg gac agg aac cag gat 729
 Leu Glu His Val Glu Arg Phe Gln Lys Met Asp Arg Asn Gln Asp
 215 220 225

gga gtg gtg acc att gat gaa ttt ctg gag act tgt cag aag gat gag 777
 Gly Val Val Thr Ile Asp Glu Phe Leu Glu Thr Cys Gln Lys Asp Glu
 230 235 240

aac atc atg aac tcc atg cag ctg ttt gag aac gtc atc taggacatgt 826
 Asn Ile Met Asn Ser Met Gln Leu Phe Glu Asn Val Ile
 245 250 255

gggaggggac cccagtggc attgcttctc aacccagaga agcctcaatc ctgacaggag 886
 aagcctctat gagaaacatt ttctaatat atttgcaaaa agtgagcagt ttacttccaa 946

03630756-002700

gacacagcca ccgtoacaca cagacacaga catacagaca cacacacaca cacacacaca 1006
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<210> 36

<211> 256

<212> PRT

<213> *Mus musculus*

<400> 36

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1 5 10 15

Gly Asp Pro Gly Arg Ile Pro Leu Ser Lys Arg Glu Ser Ile Lys Trp
20 25 30

Gln Arg Pro Arg Phe Thr Arg Gln Ala Leu Met Arg Cys Cys Leu Ile
35 40 45

Lys Trp Ile Leu Ser Ser Ala Ala Pro Gln Gly Ser Asp Ser Ser Asp
50 55 60

Ser Glu Leu Glu Leu Ser Thr Val Arg His Gln Pro Glu Gly Leu Asp
65 70 75 80

Gln Leu Gln Ala Gln Thr Lys Phe Thr Lys Lys Glu Leu Gln Ser Leu
85 90 95

Tyr Arg Gly Phe Lys Asn Glu Cys Pro Thr Gly Leu Val Asp Glu Asp
100 105 110

Thr Phe Lys Leu Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ala Thr
115 120 125

Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Ala Asp Gly Asn Gly
130 135 140

Ala Ile His Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg
145 150 155 160

Gly Thr Val His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile
165 170 175

Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys
180 185 190

Ser Ile Tyr Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu
195 200 205

Asp Ala Pro Leu Glu His Val Glu Arg Phe Phe Gln Lys Met Asp Arg
210 215 220

Asn Gln Asp Gly Val Val Thr Ile Asp Glu Phe Leu Glu Thr Cys Gln
225 230 235 240

Lys Asp Glu Asn Ile Met Asn Ser Met Gln Leu Phe Glu Asn Val Ile
245 250 255

<210> 37

<211> 531

<212> DNA

<213> *Homo sapiens*

<220>

<221> CDS

00670756.002700

<222> {1}..{336}

<220>

<223> At position 495, n=any amino acid

<400> 37

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 1 5 10 15

ggc ggt ttc ctg tac gct cag aac agc acc aag cgc agc att aaa gag 96
 Gly Gly Phe Leu Tyr Ala Gln Asn Ser Thr Lys Arg Ser Ile Lys Glu
 20 25 30

cgg ctc atg aag ctc ttg ccc tgc tca gct gcc aaa acg tcg tct cct 144
 Arg Leu Met Lys Leu Leu Pro Cys Ser Ala Ala Lys Thr Ser Ser Pro
 35 40 45

gct att caa aac agc gtg gaa gat gaa ctg gag atg gcc acc gtc agg 192
 Ala Ile Gln Asn Ser Val Glu Asp Glu Leu Glu Met Ala Thr Val Arg
 50 55 60

cat cgg ccc gaa gcc ctt gag ctt ctg gaa gcc cag agc aaa ttt acc 240
 His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys Phe Thr
 65 70 75 80

aag aaa gag ctt cag atc ctt tac aga gga ttt aag aac gta aga act 288
 Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Val Arg Thr
 85 90 95

ttc ttt ttg act tta cct tca cac aat tcc cag agg agc att gag aaa 336
 Phe Phe Leu Thr Leu Pro Ser His Asn Ser Gln Arg Ser Ile Glu Lys
 100 105 110

tgagaggaaa agggggaaaa tatcccatc tatgagaagc cccatcatat gtatatattca 396

tactgatcct tccagatag gaatataatc agtatctgtg gactttgaat ctctgtggca 456

cacccatgct ggcatactgt aattgcccat taaacaaana gtttttgaga aaaaaaaaaa 516

aaaaaaaaaa aaaaaa 531

<210> 38

<211> 112

<212> PRT

<213> Homo sapiens

<400> 38

His Glu Val Glu Ser Ile Ser Ala Gln Leu Glu Glu Ala Ser Ser Thr
 1 5 10 15

Gly Gly Phe Leu Tyr Ala Gln Asn Ser Thr Lys Arg Ser Ile Lys Glu
 20 25 30

Arg Leu Met Lys Leu Leu Pro Cys Ser Ala Ala Lys Thr Ser Ser Pro
 35 40 45

Ala Ile Gln Asn Ser Val Glu Asp Glu Leu Glu Met Ala Thr Val Arg
 50 55 60

00670756-002700

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His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys Phe Thr
 65              70              75              80

Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Val Arg Thr
              85              90              95

Phe Phe Leu Thr Leu Pro Ser His Asn Ser Gln Arg Ser Ile Glu Lys
      100              105              110

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<210> 39
<211> 2176
<212> DNA
<213> Homo sapiens

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<220>
<221> CDS
<222> (2)..(124)

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<400> 39
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  Glu Arg Phe Phe Glu Lys Met Asp Arg Asn Gln Asp Gly Val Val Thr
   1              5              10              15

att gaa gag ttc ctg gag gcc tgt cag aag gat gag aac atc atg agc 97
  Ile Glu Glu Phe Leu Glu Ala Cys Gln Lys Asp Glu Asn Ile Met Ser
           20              25              30

tcc atg cag ctg ttt gag aat gtc atc taggacacgt ccaaaggagt 144
  Ser Met Gln Leu Phe Glu Asn Val Ile
           35              40

gcatggccac agccacctcc acccccaaga aacctccatc ctgccaggag cagcctccaa 204
gaaactttta aaaaatagat ttgcaaaaag tgaacagatt gctacacaca cacacacaca 264
cacacacaca cacacacaca cacagccatt catctggggt ggagagggg acagagtcca 324
gggagggggt gagtctgggt aggggcccag tocaggagcc ccagccagcc ctteccaggc 384
cagcgaggcg aggcctgcctc tgggtgagtg gctgacagag caggctctga ggccaccagc 444
tgctggatgt caccaagaag gggctcgagt gccctgcag gggaggggtcc aatctccggt 504
gtgagccccc ctgcgtccgt tctccattct gctttcttgc cacacagtgg gccggcccca 564
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ccctcacctc aggaccccag agggaccagc tggggggcag gggggagagg gggtaattga 684
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ttgggtctgt gtggagaatc tgagggcaact ctctgccacc tccacagggt gggatgagcc 924
tctccttgcc ccagtccttg ttcagtggga atgcagtggg tggggctgta cacacctcc 984
agcacagact gttccctcca aggtcctctt aggtcccggg aggaacgtgg ttcagagact 1044

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03670736 3667 03

ggcagccagg gagccccggg cagagctcag aggagctctg gaaggggcgt gtcctctctc 1104
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 tcaccaccac accctgcgc gccttgacct tggggccaga ctggtgcac agcccaacca 2004
 ggaggggtct gcctccacg ctgggacaca gaccggccgc atgtctgcat ggcagaagcg 2064
 tctcccttgg ccacggcctg ggaggggtgt tcctgttctc agcatccact aatattcagt 2124
 cctgtatatt ttaataaaat aaacttgaca aaggaaaaaa aaaaaaaaaa aa 2176

<210> 40

<211> 41

<212> PRT

<213> Homo sapiens

<400> 40

Glu Arg Phe Phe Glu Lys Met Asp Arg Asn Gln Asp Gly Val Val Thr
 1 5 10 15

Ile Glu Glu Phe Leu Glu Ala Cys Gln Lys Asp Glu Asn Ile Met Ser
 20 25 30

Ser Met Gln Leu Phe Glu Asn Val Ile
 35 40

<210> 41

<211> 2057

<212> DNA

<213> Rattus sp.

0067056 002700

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<221> CDS		
<222> (208)..(963)		
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tctctaaaga	aaagccttgc cagccctac tcccggcccc caacccagc aggtgcgtgc	120
gccgccaggg	ggcgtgtgt gagcgcccta ttctggccac ccggcgcccc etcccacggc	180
ccaggcggga	gcggggcgcc gggggccc atg cgg ggc caa ggc aga aag gag agt	234
	Met Arg Gly Gln Gly Arg Lys Glu Ser	
	1 5	
ttg tcc gaa tcc cga gat ctg gac ggc tcc tat gac cag ctt acg ggc		282
Leu Ser Glu Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Gly		
10 15 20 25		
cac cct cca ggg ccc agt aaa aaa gcc ctg aag cag cgt ttc aag		330
His Pro Pro Gly Ser Ser Lys Lys Ala Leu Lys Gln Arg Phe Leu Lys		
	30 35 40	
ctg ctg ccg tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aac		378
Leu Leu Pro Cys Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Asn		
	45 50 55	
agc gta gag gat gag ttt gaa tta tcc acg gtg tgt cac cga cct gag		426
Ser Val Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu		
	60 65 70	
ggc ctg gaa caa ctc cag gaa cag acc aag ttc aca cgc aga gag ctg		474
Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu		
	75 80 85	
cag gtc ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg att gtc		522
Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val		
	90 95 100 105	
aac gag gag aac ttc aag cag att tat tct cag ttc ttt ccc caa gga		570
Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly		
	110 115 120	
gac tcc agc aac tat gct act ttt ctc ttc aat gcc ttt gac acc aac		618
Asp Ser Ser Ser Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn		
	125 130 135	
cac gat ggc tct gtc agt ttt gag gac ttt gtg gct ggt ttg tcg gtg		666
His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val		
	140 145 150	
att ctt ccg ggg acc ata gat gat aga ctg agc tgg gct ttc aac tta		714
Ile Leu Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu		
	155 160 165	
tat gac ctc aac aag gac ggc tgt atc aca aag gag gaa atg ctt gac		762
Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp		
	170 175 180 185	
att atg aag tcc atc tat gac atg atg ggc aag tac aca tac cct gcc		810
Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala		

[illegible]

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<210> 42
<211> 252
<212> PRT
<213> Rattus sp.
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<400> 42

<223> Xaas at positions 3,4,7,8,16,18-20,23 and 24 may
be any amino acid

09676R-050

<220>

<223> Description of Artificial Sequence: consensus motif

<400> 43

Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Lys Asp Gly Asp Gly Xaa
 1 5 10 15

Xaa Xaa Xaa Xaa Glu Phe Xaa Xaa Xaa Xaa
 20 25

<210> 44

<211> 40

<212> DNA

<213> Rattus sp.

<400> 44

taatacgact cactataggg actggccatc ctgctctcag 40

<210> 45

<211> 40

<212> DNA

<213> Rattus sp.

<400> 45

attaaccctc actaaaggga cactactgtt taagctcaag 40

<210> 46

<211> 40

<212> DNA

<213> Rattus sp.

<400> 46

taatacgact cactataggg cacctcccct cggctgttc 40

<210> 47

<211> 40

<212> DNA

<213> Rattus sp.

<400> 47

attaaccctc actaaaggga gagcagcagc atggcagggt 40

<210> 48

<211> 2413

<212> DNA

<213> Simian sp.

<220>

<221> CDS

<222> (265)..(963)

<400> 48

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[illegible]

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 Lys Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Glu Asn Val Ile
 220 225 230

 taacttgtca actagatcct gaatccaaca gacaaatgtg aactatttcta ccacctttaa 1023
 agtcggagctt accactttta gcatagattg ctacagcttga cactgaagca tattatgcaa 1083
 acaagctttg ttttaatata aagcaatccc caaaagattt gagttttcta gttataaaatt 1143
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 gaatatccaa aagtaataga atctggcata tagttttatt gattccttag ccattgggatt 1263
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 aaacaaacag caagcaaat tcactttgaa agcaccagtg gttccattac attgacaact 1983
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 gtagtaacat acatgtacac tgaattttgc catcgctgtt ttgtgtaaac tcaatgtgca 2343
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 aaaaaaaaaa 2413

<210> 49
 <211> 233
 <212> PRT
 <213> Simian sp.

05570756-002700

<400> 49

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 1 5 10 15

Val Val Ile Ile Cys Ala Ser Leu Lys Leu Leu His Leu Leu Gly Leu
 20 25 30

Ile Asp Phe Ser Glu Asp Ser Val Glu Asp Glu Leu Glu Met Ala Thr
 35 40 45

Val Arg His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys
 50 55 60

Phe Thr Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Glu
 65 70 75 80

Cys Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Glu Ile Tyr Ser
 85 90 95

Gln Phe Phe Pro Gln Gly Asp Ser Thr Thr Tyr Ala His Phe Leu Phe
 100 105 110

Asn Ala Phe Asp Thr Asp His Asn Gly Ala Val Ser Phe Glu Asp Phe
 115 120 125

Ile Lys Gly Leu Ser Ile Leu Leu Arg Gly Thr Val Gln Glu Lys Leu
 130 135 140

Asn Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Thr
 145 150 155 160

Lys Glu Glu Met Leu Asp Ile Met Lys Ala Ile Tyr Asp Met Met Gly
 165 170 175

Lys Cys Thr Tyr Pro Val Leu Lys Glu Asp Ala Pro Arg Gln His Val
 180 185 190

Glu Thr Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Val Val Thr
 195 200 205

Ile Asp Glu Phe Ile Glu Ser Cys Gln Lys Asp Glu Asn Ile Met Arg
 210 215 220

Ser Met Gln Leu Phe Glu Asn Val Ile
 225 230

<210> 50

<211> 1591

<212> DNA

<213> Simian sp.

<220>

<221> CDS

<222> (265)..(963)

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03670756.092700

09670756-092700

ttt aca gac ata tgc aaa ggg tca gga tat cta tcc tcc agt ata tgt 963
Phe Thr Asp Ile Cys Lys Gly Ser Gly Tyr Leu Ser Ser Ile Cys
220 225 230

taatgcttaa taacaagtaa tctaacagc attaaaggcc aaatctgtcc tctttccctt 1023
gacttcctta cagcatgttt atattacaag ccattcaggg acaagaagaa ctgactacc 1083
ccactgtcta ctaggaacaa acaaacagca agcaaaatc actttgaaag caccagtggc 1143
tccattacat tgacaactac taccaagatt cagtagaaaa taagtgtca acaactaatc 1203
cagattacaa tatgatttag tgcacataa aattccaaca attcagatta ttttaataca 1263
tctcagccac aactgtaaag ttgccacatt actaaagaca cacacatcgt cctgttttg 1323
tagaaatatc acaaagacca agagggtaca gaaggaggaa atttgcaact gtccttgcaa 1383
caataaatca ggtatctatt ctgggtgtaga gataggatgt tgaaagctgc cctgctatca 1443
ccagtgtaga aattaagagt agtacaatac atgtacactg aaatttgccā tgcgctgttt 1503
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gttawaaamw mwaaaaaaaa aaaaaaaa 1591

<210> 51
<211> 233
<212> PRT
<213> Simian sp.

<400> 51
Met Leu Thr Leu Glu Trp Glu Ser Glu Gly Leu Gln Thr Val Gly Ile
1 5 10 15

Val Val Ile Ile Cys Ala Ser Leu Lys Leu Leu His Leu Leu Gly Leu
20 25 30

Ile Asp Phe Ser Glu Asp Ser Val Glu Asp Glu Leu Glu Met Ala Thr
35 40 45

Val Arg His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys
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Phe Thr Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Glu
65 70 75 80

Cys Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Glu Ile Tyr Ser
85 90 95

Gln Phe Phe Pro Gln Gly Asp Ser Thr Thr Tyr Ala His Phe Leu Phe
100 105 110

Asn Ala Phe Asp Thr Asp His Asn Gly Ala Val Ser Phe Glu Asp Phe
115 120 125

Ile Lys Gly Leu Ser Ile Leu Leu Arg Gly Thr Val Gln Glu Lys Leu
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	Met Asn Gly Val Glu Gly Asn Asn Glu
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ctc cct ctc gct aac acc tcg acc tcc gcc ctt gtc ccg gaa gat ctg 159	
Leu Pro Leu Ala Asn Thr Ser Thr Ser Ala Leu Val Pro Glu Asp Leu 25	
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gat ctg aag caa gac cag ccg ctc agc gag gaa act gac acg gtg cgg 207	
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Gly Cys Ala Ala Ala Ala Gly Glu Gly Leu Glu Asp Gly Leu Ser Ser 85	
75 80 85	
tca aag tgt ggg gac gca ccc ttg gcg tct gtg gca gcc aac gac agc 399	
Ser Lys Cys Gly Asp Ala Pro Leu Ala Ser Val Ala Ala Asn Asp Ser 105	
90 95 100 105	
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Asn Lys Asn Gly Cys Gln Leu Ala Gly Pro Leu Ser Pro Ala Lys Pro 115 120	
110 115 120	

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 Lys Thr Leu Glu Ala Ser Gly Ala Val Gly Leu Gly Ser Gln Met Met
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cca ggg ccg aag aag acc aag gta atg act acc aag ggc gcc atc tct 543
 Pro Gly Pro Lys Lys Thr Lys Val Met Thr Thr Lys Gly Ala Ile Ser
 140 145 150

gcg act aca ggc aag gaa gga gaa gca ggg gcg gca atg cag gaa aag 591
 Ala Thr Thr Gly Lys Glu Gly Glu Ala Gly Ala Met Gln Glu Lys
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aag ggg gtg cag aaa gaa aaa aag gca gct gga gga ggg aaa gac gag 639
 Lys Gly Val Gln Lys Glu Lys Lys Ala Ala Gly Gly Gly Lys Asp Glu
 170 175 180 185

act cgt cct aga gcc cct aag atc aat aac tgc atg gac tcc ctg gaa 687
 Thr Arg Pro Arg Ala Pro Lys Ile Asn Asn Cys Met Asp Ser Leu Glu
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gcc atc gat caa gag ctg tca aat gta aat gcg caa gct gac agg gcc 735
 Ala Ile Asp Gln Glu Leu Ser Asn Val Asn Ala Gln Ala Asp Arg Ala
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ttc ctc cag ctg gaa cgc aaa ttt ggg cgg atg aga agg ctc cac atg 783
 Phe Leu Gln Leu Glu Arg Lys Phe Gly Arg Met Arg Leu His Met
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cag cgc cga agt ttc atc atc caa aac atc cca ggt ttc tgg gtc aca 831
 Gln Arg Arg Ser Phe Ile Ile Gln Asn Ile Pro Gly Phe Trp Val Thr
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 Glu Asp Met Met Arg Tyr Met Ile Asn Leu Glu Val Glu Glu Leu Lys
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cac cca aga gca ggg tgc aaa ttt aag ttc atc ttc caa agc aac ccc 975
 His Pro Arg Ala Gly Cys Lys Phe Lys Phe Ile Phe Gln Ser Asn Pro
 285 290 295

tac ttc cga aat gag ggg ctg gtc aaa gag tac gag cgc aga tcc tca 1023
 Tyr Phe Arg Asn Glu Gly Leu Val Lys Glu Tyr Glu Arg Ser Ser
 300 305 310

ggt cga gtg gtg tcg ctc tct acg cca atc cgc tgg cac cgg ggt caa 1071
 Gly Arg Val Val Ser Leu Ser Thr Pro Ile Arg Trp His Arg Gly Gln
 315 320 325

gaa ccc cag gcc cat atc cac agg aat aga gag ggg aac acg att ccc 1119
 Glu Pro Gln Ala His Ile His Arg Asn Arg Glu Gly Asn Thr Ile Pro
 330 335 340 345

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 365 370 375

tac ctg atg ggc gat ggg cca cgc aga gga gtt cga gtc cca cca agg 1263
 Tyr Leu Met Gly Asp Gly Pro Arg Arg Gly Val Arg Val Pro Pro Arg
 380 385 390

cag cca gtg gag agt ccc agg tcc ttc agg ttc cag tct ggc 1305
 Gln Pro Val Glu Ser Pro Arg Ser Phe Arg Phe Gln Ser Gly
 395 400 405

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 35 40 45

Ala Gly Ala Glu Gly Gly Ala Ser Pro Asp Ser Glu His Cys Asp Pro
 50 55 60

Gln Leu Cys Leu Arg Val Ala Glu Asn Gly Cys Ala Ala Ala Ala Gly
 65 70 75 80

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Ala	Gly	Pro	Leu	Ser	Pro	Ala	Lys	Pro	Lys	Thr	Leu	Glu	Ala	Ser	Gly	
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Ala	Val	Gly	Leu	Gly	Ser	Gln	Met	Met	Pro	Gly	Pro	Lys	Lys	Thr	Lys	
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Val	Met	Thr	Thr	Lys	Gly	Ala	Ile	Ser	Ala	Thr	Thr	Gly	Lys	Glu	Gly	
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Glu	Ala	Gly	Ala	Ala	Met	Gln	Glu	Lys	Lys	Gly	Val	Gln	Lys	Glu	Lys	
				165					170					175		
Lys	Ala	Ala	Gly	Gly	Gly	Lys	Asp	Glu	Thr	Arg	Pro	Arg	Ala	Pro	Lys	
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Ile	Asn	Asn	Cys	Met	Asp	Ser	Leu	Glu	Ala	Ile	Asp	Gln	Glu	Leu	Ser	
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Asn	Val	Asn	Ala	Gln	Ala	Asp	Arg	Ala	Phe	Leu	Gln	Leu	Glu	Arg	Lys	
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Phe	Gly	Arg	Met	Arg	Arg	Leu	His	Met	Gln	Arg	Arg	Ser	Phe	Ile	Ile	
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Gln	Asn	Ile	Pro	Gly	Phe	Trp	Val	Thr	Ala	Phe	Arg	Asn	His	Pro	Gln	
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Leu	Ser	Pro	Met	Ile	Ser	Gly	Gln	Asp	Glu	Asp	Met	Met	Arg	Tyr	Met	
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Ile	Asn	Leu	Glu	Val	Glu	Glu	Leu	Lys	His	Pro	Arg	Ala	Gly	Cys	Lys	
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Val	Lys	Glu	Tyr	Glu	Arg	Arg	Ser	Ser	Gly	Arg	Val	Val	Ser	Leu	Ser	
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				370					375					380		
Arg	Arg	Gly	Val	Arg	Val	Pro	Pro	Arg	Gln	Pro	Val	Glu	Ser	Pro	Arg	
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Leu Pro Leu Ala Gln Thr Gly Gly Leu Ala Ala Pro Asp His Ala Ser 25															
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Arg Val Pro Val Ala Gly Ser Arg Gly Gly Ala Ala Thr Lys Ala Gly 75															
80 85															
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Gln Glu Asp Ala Pro Pro Thr Lys Gly Leu Glu Ala Ala Ser Ala 90															
95 100 105															
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2025 RELEASE UNDER E.O. 14176

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Thr Gly Gly Gly Ser Leu Glu Thr Val Ala Glu Gly Gly Ala Ser Gln
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Asp Pro Val Asp Cys Gly Pro Ala Leu Arg Val Pro Val Ala Gly Ser
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Arg Gly Gly Ala Ala Thr Lys Ala Gly Gln Glu Asp Ala Pro Pro Ser
 85 90 95

Thr Lys Gly Leu Glu Ala Ala Ser Ala Ala Glu Ala Ala Asp Ser Ser
 100 105 110

Gln Lys Asn Gly Cys Gln Leu Gly Glu Pro Arg Gly Pro Ala Gly Gln
 115 120 125

 Lys Ala Leu Glu Ala Cys Gly Ala Gly Gly Leu Gly Ser Gln Met Ile
 130 135 140

 Pro Gly Lys Lys Ala Lys Glu Val Thr Thr Lys Lys Arg Ala Ile Ser
 145 150 155 160

 Ala Ala Val Glu Lys Glu Gly Glu Ala Gly Ala Ala Met Glu Glu Lys
 165 170 175

 Lys Val Val Gln Lys Glu Lys Lys Val Ala Gly Gly Val Lys Glu Glu
 180 185 190

 Thr Arg Pro Arg Ala Pro Lys Ile Asn Asn Cys Met Asp Ser Leu Glu
 195 200 205

 Ala Ile Asp Gln Glu Leu Ser Asn Val Asn Ala Gln Ala Asp Arg Ala
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 Phe Leu Gln Leu Glu Arg Lys Phe Gly Arg Met Arg Arg Leu His Met
 225 230 235 240

 Gln Arg Arg Ser Phe Ile Ile Gln Asn Ile Pro Gly Phe Trp Val Thr
 245 250 255

 Ala Phe Arg Asn His Pro Gln Leu Ser Pro Met Ile Ser Gly Gln Asp
 260 265 270

 Glu Asp Met Leu Arg Tyr Met Ile Asn Leu Glu Val Glu Glu Lys
 275 280 285

 His Pro Arg Ala Gly Cys Lys Phe Lys Phe Ile Phe Gln Gly Asn Pro
 290 295 300

 Tyr Phe Arg Asn Glu Gly Leu Val Lys Glu Tyr Glu Arg Arg Ser Ser
 305 310 315 320

 Gly Arg Val Val Ser Leu Ser Thr Pro Ile Arg Trp His Arg Gly Gln
 325 330 335

 Asp Pro Gln Ala His Ile His Arg Asn Arg Glu Gly Asn Thr Ile Pro
 340 345 350

 Ser Phe Phe Asn Trp Phe Ser Asp His Ser Leu Leu Glu Phe Asp Arg
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 Ile Ala Glu Ile Ile Lys Gly Glu Leu Trp Pro Asn Pro Leu Gln Tyr
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<213> *Rattus* sp.

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Asn	His	Gly	Ser	Ala	Leu	His	Ile	Ala	Ala	Ser	Asn	Leu	Cys	Leu	Gly	
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gcc	gcc	aaa	tgt	tta	ctg	gag	cat	ggt	gcc	aac	cca	gcg	ctg	agg	aat	144
Ala	Ala	Lys	Cys	Leu	Leu	Glu	His	Gly	Ala	Asn	Pro	Ala	Leu	Arg	Asn	
		35				40					45					

cga	aaa	gga	cag	gta	cca	gcg	gaa	gtg	gtc	cca	gac	ccc	atg	gac	atg	192
Arg	Lys	Gly	Gln	Val	Pro	Ala	Glu	Val	Val	Pro	Asp	Pro	Met	Asp	Met	
	50					55					60					

tcc	ctt	gac	aag	gca	gag	gca	gcc	ctg	gtg	gcc	aag	gaa	ttg	cgg	acg	240
Ser	Leu	Asp	Lys	Ala	Glu	Ala	Ala	Leu	Val	Ala	Lys	Glu	Leu	Arg	Thr	
65				70						75				80		

ctg	cta	gaa	gag	gct	gtg	cca	ctg	tcc	tgc	acc	ctt	cct	aaa	gtc	aca	288
Leu	Leu	Glu	Glu	Ala	Val	Pro	Leu	Ser	Cys	Thr	Leu	Pro	Lys	Val	Thr	
			85						90					95		

cta	ccc	aac	tat	gac	aac	gtc	cca	ggc	aat	ctc	atg	ctc	agc	gcg	ctg	336
Leu	Pro	Asn	Tyr	Asp	Asn	Val	Pro	Gly	Asn	Leu	Met	Leu	Ser	Ala	Leu	
			100					105					110			

ggc	ctg	cgt	cta	gga	gac	cga	gtg	ctc	ctc	gat	ggc	cag	aag	acg	ggc	384
Gly	Leu	Arg	Leu	Gly	Asp	Arg	Val	Leu	Leu	Asp	Gly	Gln	Lys	Thr	Gly	
	115					120					125					

acg	ctg	agg	ttc	tgc	ggg	acc	acc	gag	ttc	gcc	agt	ggc	cag	tgg	gtg	432
Thr	Leu	Arg	Phe	Cys	Gly	Thr	Thr	Glu	Phe	Ala	Ser	Gly	Gln	Trp	Val	
	130					135					140					

ggc	gtg	gag	cta	gat	gaa	ccg	gaa	ggc	aag	aac	gac	ggc	agc	gtt	ggg	480
Gly	Val	Glu	Leu	Asp	Glu	Pro	Glu	Gly	Lys	Asn	Asp	Gly	Ser	Val	Gly	
145					150					155				160		

ggt	gtc	cgg	tac	ttc	atc	tgc	cct	ccc	aag	cag	ggt	ctc	ttt	gca	tct	528
Gly	Val	Arg	Tyr	Phe	Ile	Cys	Pro	Pro	Lys	Gln	Gly	Leu	Phe	Ala	Ser	
				165					170					175		

gtg	tcc	aag	gtc	tcc	aag	gca	gtg	gat	gca	ccc	ccc	tca	tct	gtt	acc	576
Val	Ser	Lys	Val	Ser	Lys	Ala	Val	Asp	Ala	Pro	Pro	Ser	Ser	Val	Thr	
			180					185					190			

tcc	acg	ccc	cgc	act	ccc	cgg	atg	gac	ttc	tcc	cgt	gta	acg	ggc	aaa	624
Ser	Thr	Pro	Arg	Thr	Pro	Arg	Met	Asp	Phe	Ser	Arg	Val	Thr	Gly	Lys	
		195				200						205				

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atcccaggct ctcagggcat ctcaaacctg actcccaggc accaggagac cccaacaga 2201
 aagtcaccatc ttggaacaa ggaaggact ctaataccct tagtccatgg atctttaatt 2261
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 gataactaat atgtgcaggg ccccgaggct ctaacaggac cccaaatcat ggagtcoccta 2381
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 aaaaaaaaaa aaaaaaaaaa aa 2643

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<211> 267

<212> PRT

<213> Rattus sp.

<400> 57

Leu Lys Gly Ala Arg Pro Arg Val Val Asn Ser Thr Cys Ser Asp Phe
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Asn His Gly Ser Ala Leu His Ile Ala Ala Ser Asn Leu Cys Leu Gly
 20 25 30

Ala Ala Lys Cys Leu Leu Glu His Gly Ala Asn Pro Ala Leu Arg Asn
 35 40 45

Arg Lys Gly Gln Val Pro Ala Glu Val Val Pro Asp Pro Met Asp Met
 50 55 60

Ser Leu Asp Lys Ala Glu Ala Ala Leu Val Ala Lys Glu Leu Arg Thr
 65 70 75 80

Leu Leu Glu Glu Ala Val Pro Leu Ser Cys Thr Leu Pro Lys Val Thr
 85 90 95

Leu Pro Asn Tyr Asp Asn Val Pro Gly Asn Leu Met Leu Ser Ala Leu
 100 105 110

Gly Leu Arg Leu Gly Asp Arg Val Leu Leu Asp Gly Gln Lys Thr Gly
 115 120 125

Thr Leu Arg Phe Cys Gly Thr Thr Glu Phe Ala Ser Gly Gln Trp Val
 130 135 140

Gly Val Glu Leu Asp Glu Pro Glu Gly Lys Asn Asp Gly Ser Val Gly
 145 150 155 160

Gly Val Arg Tyr Phe Ile Cys Pro Pro Lys Gln Gly Leu Phe Ala Ser
 165 170 175

Val Ser Lys Val Ser Lys Ala Val Asp Ala Pro Pro Ser Ser Val Thr
 180 185 190

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Ser Thr Pro Arg Thr Pro Arg Met Asp Phe Ser Arg Val Thr Gly Lys
195 200 205

Gly Arg Arg Glu His Lys Gly Lys Lys Ser Pro Ser Ser Pro Ser
210 215 220

Leu Gly Ser Leu Gln Gln Arg Glu Gly Ala Lys Ala Glu Val Gly Asp
225 230 235 240

Gln Val Leu Val Ala Gly Gln Asn Arg Asp Cys Ala Phe Leu Trp Glu
245 250 255

Asp Arg Leu Cys Ser Arg Leu Leu Val Trp His
260 265

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<211> 2929

<212> DNA

<213> Rattus sp.

<220>

<221> CDS

<222> (1)..(810)

<400> 58

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1 5 10 15

cgc tta gct gaa atg cct gca gat agt gga tac cct gca tac ctt ggt 96
Arg Leu Ala Glu Met Pro Ala Asp Ser Gly Tyr Pro Ala Tyr Leu Gly
20 25 30

gcc cga ctg gct tct ttc tat gag cga gca gcc aga gtg aaa tgt ctt 144
Ala Arg Leu Ala Ser Phe Tyr Glu Arg Ala Gly Arg Val Lys Cys Leu
35 40 45

gga aac cct gag aga gaa ggg agt gtc agc att gta gga gca gtt tct 192
Gly Asn Pro Glu Arg Glu Gly Ser Val Ser Ile Val Gly Ala Val Ser
50 55 60

cca cct ggt ggt gat ttt tct gat cca gtc aca tct gct act ctg ggt 240
Pro Pro Gly Gly Asp Phe Ser Asp Pro Val Thr Ser Ala Thr Leu Gly
65 70 75 80

att gtt cag gtg ttc tgg ggc ttg gat aag aag cta gct cag cgc aag 288
Ile Val Gln Val Phe Trp Gly Leu Asp Lys Lys Leu Ala Gln Arg Lys
85 90 95

cac ttc ccg tcc gtc aac tgg ctc att agc tac agc aag tac atg cgc 336
His Phe Pro Ser Val Asn Trp Leu Ile Ser Tyr Ser Lys Tyr Met Arg
100 105 110

gcc ctg gac gag tac tat gac aaa cac ttc aca gag ttc gtg cct ctg 384
Ala Leu Asp Glu Tyr Tyr Asp Lys His Phe Thr Glu Phe Val Pro Leu
115 120 125

agg acc aaa gct aag gag att ctg cag gaa gag gag gat ctg gcg gaa 432
Arg Thr Lys Ala Lys Glu Ile Leu Gln Glu Glu Asp Leu Ala Glu
130 135 140

00260-9520260

atc gtg cag ctc gtg gga aag gcg tct tta gca gag aca gat aaa atc 480
 Ile Val Gln Leu Val Gly Lys Ala Ser Leu Ala Glu Thr Asp Lys Ile
 145 150 155 160
 acc ctg gag gta gca aaa ctt atc aaa gat gac ttc cta caa caa aat 528
 Thr Leu Glu Val Ala Lys Leu Ile Lys Asp Asp Phe Leu Gln Gln Asn
 165 170 175
 ggg tac act cct tat gac agg ttc tgt cca ttc tat aag acg gtg ggg 576
 Gly Tyr Thr Pro Tyr Asp Arg Phe Cys Pro Phe Tyr Lys Thr Val Gly
 180 185 190
 atg ctg tcc aac atg att tca ttc tat gat atg gcc cgc cgg gct gtg 624
 Met Leu Ser Asn Met Ile Ser Phe Tyr Asp Met Ala Arg Arg Ala Val
 195 200 205
 gag acc acc gcc cag agt gac aat aag atc aca tgg tcc att atc cgt 672
 Glu Thr Thr Ala Gln Ser Asp Asn Lys Ile Thr Trp Ser Ile Ile Arg
 210 215 220
 gag cac atg ggg gag att ctc tat aaa ctt tcc tcc atg aaa ttc aag 720
 Glu His Met Gly Glu Ile Leu Tyr Lys Leu Ser Ser Met Lys Phe Lys
 225 230 235 240
 gat cca gtg aag gat ggc gag gca aag atc aag gcc gac tac gca cag 768
 Asp Pro Val Lys Asp Gly Glu Ala Lys Ile Lys Ala Asp Tyr Ala Gln
 245 250 255
 ctt ctt gaa gat atg cag aac gca ttc cgt agc ctg gaa gat 810
 Leu Leu Glu Asp Met Gln Asn Ala Phe Arg Ser Leu Glu Asp
 260 265 270
 tagaactgtg acttctctcc tctctctccg cagctcatat gtgtatatatt tctgaattt 870
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 cttatatatta gtcagatgag ctccagagtgg ggagggtgtg ggttagaata ccacaaggac 1650

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acgcagcagt gcctgcaggc agtggtggccg ggggccagag cggcattgtt ttcacgaggt 1710
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 agaagtaca gaaacaacgc tcagattttc acggttaact tccctctgcc cacactgtag 2610
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 gttaaacaag ttctatatgt atttttccag tgttaaactc catacctatg ccttttgaa 2790
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<211> 270

<212> PRT

<213> Rattus sp.

<400> 59

Ala Asp Ser Thr Ser Arg Trp Ala Glu Ala Leu Arg Glu Ile Ser Gly
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Arg Leu Ala Glu Met Pro Ala Asp Ser Gly Tyr Pro Ala Tyr Leu Gly
 20 25 30

Ala Arg Leu Ala Ser Phe Tyr Glu Arg Ala Gly Arg Val Lys Cys Leu
 35 40 45

Gly Asn Pro Glu Arg Glu Gly Ser Val Ser Ile Val Gly Ala Val Ser

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50 55 60
 Pro Pro Gly Gly Asp Phe Ser Asp Pro Val Thr Ser Ala Thr Leu Gly
 65 70 75
 Ile Val Gln Val Phe Trp Gly Leu Asp Lys Lys Leu Ala Gln Arg Lys
 85 90 95
 His Phe Pro Ser Val Asn Trp Leu Ile Ser Tyr Ser Lys Tyr Met Arg
 100 105 110
 Ala Leu Asp Glu Tyr Tyr Asp Lys His Phe Thr Glu Phe Val Pro Leu
 115 120 125
 Arg Thr Lys Ala Lys Glu Ile Leu Gln Glu Glu Glu Asp Leu Ala Glu
 130 135 140
 Ile Val Gln Leu Val Gly Lys Ala Ser Leu Ala Glu Thr Asp Lys Ile
 145 150 155 160
 Thr Leu Glu Val Ala Lys Leu Ile Lys Asp Asp Phe Leu Gln Gln Asn
 165 170 175
 Gly Tyr Thr Pro Tyr Asp Arg Phe Cys Pro Phe Tyr Lys Thr Val Gly
 180 185
 Met Leu Ser Asn Met Ile Ser Phe Tyr Asp Met Ala Arg Arg Ala Val
 195 200 205
 Glu Thr Thr Ala Gln Ser Asp Asn Lys Ile Thr Trp Ser Ile Ile Arg
 210 215 220
 Glu His Met Gly Glu Ile Leu Tyr Lys Leu Ser Ser Met Lys Phe Lys
 225 230 235 240
 Asp Pro Val Lys Asp Gly Glu Ala Lys Ile Lys Ala Asp Tyr Ala Gln
 245 250 255
 Leu Leu Glu Asp Met Gln Asn Ala Phe Arg Ser Leu Glu Asp
 260 265 270

 <210> 60
 <211> 1489
 <212> DNA
 <213> Rattus sp.

 <220>
 <221> CDS
 <222> (1)..(1053)

 <400> 60
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 Ala Arg Leu Pro Ala Pro Glu His Ala Arg Gln Gln Pro Leu Leu Ser
 1 5 10 15

 ggc cct gag ccc gga tcg tcc gcc ccg gtt cca gtt ccc ggc gtg gcc 96
 Gly Pro Glu Pro Gly Ser Ser Ala Arg Val Pro Val Pro Gly Val Ala
 20 25 30

 agt agg cgg cag ccg cga ggc gcc aag cca ccc agc ggg gac ggc ctg 144

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Ser Arg Arg Gln Pro Arg Gly Gly Lys Pro Pro Ser Gly Asp Gly Leu
 35 40 45

gag tcg ggc ccc tct cca cgc ccc ctt ctc cac gcg cgc ggg gag gca 192
 Glu Ser Gly Pro Ser Pro Arg Pro Leu Leu His Ala Arg Gly Glu Ala
 50 55 60

ggg ctc cac cgc cag tct gga agg gtt cca cat aca gga acg gcc tac 240
 Gly Leu His Arg Gln Ser Gly Arg Val Pro His Thr Gly Thr Ala Tyr
 65 70 75 80

ttc gca gat gag ccc acc gag gct cag gct ccg ggc gga ttc tgc gtg 288
 Phe Ala Asp Glu Pro Thr Glu Ala Gln Ala Pro Gly Gly Phe Cys Val
 85 90 95

tca ccc tcg ctc ctt ggg gtc cgc tgg ccg gcc tgt gcc acc cgg acg 336
 Ser Pro Ser Leu Leu Gly Val Arg Trp Pro Ala Cys Ala Thr Arg Thr
 100 105 110

ccc ggc tca ctg cct ctg tct ccc cca tca gcg cag ccc cgg acg cta 384
 Pro Gly Ser Leu Pro Leu Ser Pro Pro Ser Ala Gln Pro Arg Thr Leu
 115 120 125

tgg ccc acc cct cca gct ggc ccc tcg agt agg atg gta gca cgt aac 432
 Trp Pro Thr Pro Pro Ala Gly Pro Ser Ser Arg Met Val Ala Arg Asn
 130 135 140

cag gtg gca gcc gac aat gcg atc tcc ccg gca tca gag ccc cga cgg 480
 Gln Val Ala Ala Asp Asn Ala Ile Ser Pro Ala Ser Glu Pro Arg Arg
 145 150 155 160

cgg cca gag cca tcc tcg tcc tcg tct tcg tcc tcg ccg gcg gcc ccg 528
 Arg Pro Glu Pro Ser Ser Ser Ser Ser Ser Ser Pro Ala Ala Pro
 165 170 175

gcg cgt ccc cgg ccc tgc ccg gtg gtc ccg gcc ccg gct ccg ggc gac 576
 Ala Arg Pro Arg Pro Cys Pro Val Val Pro Ala Pro Ala Pro Gly Asp
 180 185 190

act cac ttc cgc acc ttc cgc tcc cac tct gat tac ccg cgc atc acg 624
 Thr His Phe Arg Thr Phe Arg Ser His Ser Asp Tyr Arg Arg Ile Thr
 195 200 205

cgg acc agc gct ctc ctg gac gcc tgc ggc ttc tac tgg gga ccc ctg 672
 Arg Thr Ser Ala Leu Leu Asp Ala Cys Gly Phe Tyr Trp Gly Pro Leu
 210 215 220

agc gtg cat ggg gcg cac gaa cgg ctg cgt gcc gag ccc gtg gcc acc 720
 Ser Val His Gly Ala His Glu Arg Leu Arg Ala Glu Pro Val Gly Thr
 225 230 235 240

ttc ttg gtg cgc gac agt cgc cag cgg aac tgc ttc ttc gcg ctc agc 768
 Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys Phe Phe Ala Leu Ser
 245 250 255

gtg aag atg gct tcg ggc ccc acg agc att cgt gtg cac ttc cag gcc 816
 Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg Val His Phe Gln Ala
 260 265 270

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ggc cgc ttc cac ctg gac ggc agc cgc gag acc ttc gac tgc ctc ttc 864
 Gly Arg Phe His Leu Asp Gly Ser Arg Glu Thr Phe Asp Cys Leu Phe
 275 280 285

gag ctg ctg gag cac tac gtg gcg gcg ccg cgc cgc atg ttg ggg gcc 912
 Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg Arg Met Leu Gly Ala
 290 295 300

cca ctg cgc cag cgc cgc gtg cgg ccg ctg cag gag ctg tgt cgc cag 960
 Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln Glu Leu Cys Arg Gln
 305 310 315 320

cgc atc gtg gcc gcc gtg ggt cgc gag aac ctg gca cgc atc cct ctt 1008
 Arg Ile Val Ala Ala Val Gly Arg Glu Asn Leu Ala Arg Ile Pro Leu
 325 330 335

aac ccg gta ctc cgt gac tac ctg agt tcc ttc ccc ttc cag atc 1053
 Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe Pro Phe Gln Ile
 340 345 350

tgaccggctg ccgccgtgcc cgcagcatta agtgggagcg cettattatt tcttattatt 1113
 aattattatt atttttctgg aaccacgtgg gageccctccc ccctaggtc ggaggagggtg 1173
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 gcctcccctc ctggtgtccc ctcccgtccc cccgtggtgt agcagcttgt gtcctggggcc 1293
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 aaaaaaaaa aaaaaa 1489

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 <211> 351
 <212> FRT
 <213> Rattus sp.

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 20 25 30

Ser Arg Arg Gln Pro Arg Gly Gly Lys Pro Pro Ser Gly Asp Gly Leu
 35 40 45

Glu Ser Gly Pro Ser Pro Arg Pro Leu Leu His Ala Arg Gly Glu Ala
 50 55 60

Gly Leu His Arg Gln Ser Gly Arg Val Pro His Thr Gly Thr Ala Tyr
 65 70 75 80

Phe Ala Asp Glu Pro Thr Glu Ala Gln Ala Pro Gly Gly Phe Cys Val
 85 90 95

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Ser	Pro	Ser	Leu	Leu	Gly	Val	Arg	Trp	Pro	Ala	Cys	Ala	Thr	Arg	Thr
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Pro	Gly	Ser	Leu	Pro	Leu	Ser	Pro	Pro	Ser	Ala	Gln	Pro	Arg	Thr	Leu
		115					120					125			
Trp	Pro	Thr	Pro	Pro	Ala	Gly	Pro	Ser	Ser	Arg	Met	Val	Ala	Arg	Asn
	130					135					140				
Gln	Val	Ala	Ala	Asp	Asn	Ala	Ile	Ser	Pro	Ala	Ser	Glu	Pro	Arg	Arg
	145				150					155					160
Arg	Pro	Glu	Pro	Ser	Ser	Ser	Ser	Ser	Ser	Ser	Ser	Pro	Ala	Ala	Pro
				165					170					175	
Ala	Arg	Pro	Arg	Pro	Cys	Pro	Val	Val	Pro	Ala	Pro	Ala	Pro	Gly	Asp
			180					185					190		
Thr	His	Phe	Arg	Thr	Phe	Arg	Ser	His	Ser	Asp	Tyr	Arg	Arg	Ile	Thr
	195						200					205			
Arg	Thr	Ser	Ala	Leu	Leu	Asp	Ala	Cys	Gly	Phe	Tyr	Trp	Gly	Pro	Leu
	210					215					220				
Ser	Val	His	Gly	Ala	His	Glu	Arg	Leu	Arg	Ala	Glu	Pro	Val	Gly	Thr
	225				230					235				240	
Phe	Leu	Val	Arg	Asp	Ser	Arg	Gln	Arg	Asn	Cys	Phe	Phe	Ala	Leu	Ser
				245					250					255	
Val	Lys	Met	Ala	Ser	Gly	Pro	Thr	Ser	Ile	Arg	Val	His	Phe	Gln	Ala
			260					265					270		
Gly	Arg	Phe	His	Leu	Asp	Gly	Ser	Arg	Glu	Thr	Phe	Asp	Cys	Leu	Phe
		275					280					285			
Glu	Leu	Leu	Glu	His	Tyr	Val	Ala	Ala	Pro	Arg	Arg	Met	Leu	Gly	Ala
	290					295					300				
Pro	Leu	Arg	Gln	Arg	Arg	Val	Arg	Pro	Leu	Gln	Glu	Leu	Cys	Arg	Gln
	305				310					315					320
Arg	Ile	Val	Ala	Ala	Val	Gly	Arg	Glu	Asn	Leu	Ala	Arg	Ile	Pro	Leu
			325						330					335	
Asn	Pro	Val	Leu	Arg	Asp	Tyr	Leu	Ser	Ser	Phe	Pro	Phe	Gln	Ile	
			340					345					350		

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agtgggagcg ccttattatt tcttattatt aattattatt atttttctgg aaccacgtgg 855
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 ggctggagac cttatccgc ctctcgggg gccctccctc ctggtgctcc ctcccggtcc 975
 ccctgggtgt agcagcttgt gtctggggcc aggacctgaa ctccacgcct acctctccat 1035
 gtttacatgt tccagtatc tttgcacaaa ccagggggtgg gggaggggtct ctggtctcat 1095
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 Ser Pro Ala Ala Pro Ala Arg Pro Arg Pro Cys Pro Val Val Pro Ala
 35 40 45
 Pro Ala Pro Gly Asp Thr His Phe Arg Thr Phe Arg Ser His Ser Asp
 50 55 60
 Tyr Arg Arg Ile Thr Arg Thr Ser Ala Leu Leu Asp Ala Cys Gly Phe
 65 70 75 80
 Tyr Trp Gly Pro Leu Ser Val His Gly Ala His Glu Arg Leu Arg Ala
 85 90 95
 Glu Pro Val Gly Thr Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys
 100 105 110
 Phe Phe Ala Leu Ser Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg
 115 120 125
 Val His Phe Gln Ala Gly Arg Phe His Leu Asp Gly Ser Arg Glu Thr
 130 135 140
 Phe Asp Cys Leu Phe Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg
 145 150 155 160
 Arg Met Leu Gly Ala Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln
 165 170 175
 Glu Leu Cys Arg Gln Arg Ile Val Ala Ala Val Gly Arg Glu Asn Leu
 180 185 190
 Ala Arg Ile Pro Leu Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe
 195 200 205
 Pro Phe Gln Ile

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His Arg Phe Ala Gly Glu Lys Asn Tyr Leu Thr Lys Glu Asp Leu Arg
 20 25 30

Val Leu Met Glu Arg Glu Phe Pro Gly Phe Leu Glu Asn Gln Lys Asp
 35 40 45

Pro Leu Ala Val Asp Lys Ile Met Lys Asp Leu Asp Gln Cys Arg Asp
 50 55 60

Gly Lys Val Gly Phe Gln Ser Phe Leu Ser Leu Val Ala Gly Leu Ile
 65 70 75 80

Ile Ala Cys Asn Asp Tyr Phe Val Val His Met Lys Gln Lys Lys
 85 90 95

<210> 66

<211> 639

<212> DNA

<213> Rattus sp.

<220>

<221> CDS

<222> (1)..(636)

<400> 66

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Met Ala Tyr Ala Tyr Leu Phe Lys Tyr Ile Ile Ile Gly Asp Thr Gly	
1 5 10 15	
ggt ggt aaa tcg tgc tta ttg cta cag ttt aca gac aag agg ttt cag	96
Val Gly Lys Ser Cys Leu Leu Leu Gln Phe Thr Asp Lys Arg Phe Gln	
20 25 30	
cag gtg cat gac ctc aca att ggt gta gag ttt ggt gct cga atg ata	144
Pro Val His Asp Leu Thr Ile Gly Val Glu Phe Gly Ala Arg Met Ile	
35 40 45	
acc att gat ggg aaa cag ata aaa ctc cag atc tgg gat aca gca ggg	192
Thr Ile Asp Gly Lys Gln Ile Lys Leu Gln Ile Trp Asp Thr Ala Gly	
50 55 60	
cag gag tcc ttt cgt tct atc aca agg tca tat tac aga ggt gca ggc	240
Gln Glu Ser Phe Arg Ser Ile Thr Arg Ser Tyr Tyr Arg Gly Ala Ala	
65 70 75 80	
ggg gct tta cta gtg tat gat att aca agg aga gac acg ttc aac cac	288
Gly Ala Leu Leu Val Tyr Asp Ile Thr Arg Arg Asp Thr Phe Asn His	
85 90 95	
ttg aca acc tgg tta gaa gac gcc cgt cag cat tcc aat tcc aac atg	336
Leu Thr Thr Trp Leu Glu Asp Ala Arg Gln His Ser Asn Ser Asn Met	
100 105 110	
gtc atc atg ctt att gga aat aaa agt gac tta gaa tct agg aga gaa	384
Val Ile Met Leu Ile Gly Asn Lys Ser Asp Leu Glu Ser Arg Arg Glu	
115 120 125	
gtg aaa aag gaa gaa ggt gaa gct ttt gca cga gag cat gga ctt atc	432
Val Lys Lys Glu Glu Gly Glu Ala Phe Ala Arg Glu His Gly Leu Ile	
130 135 140	

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ttc atg gaa act tct gcc aag act gct tct aat gta gag gag gca ttt 480
 Phe Met Glu Thr Ser Ala Lys Thr Ala Ser Asn Val Glu Glu Ala Phe
 145 150 155 160

 att aac aca gca aaa gaa att tat gaa aaa atc caa gaa ggg gtc ttt 528
 Ile Asn Thr Ala Lys Glu Ile Tyr Glu Lys Ile Gln Glu Gly Val Phe
 165 170 175

 gac att aat aat gag gca aac ggc atc aaa att ggc cct cag cat gct 576
 Asp Ile Asn Asn Glu Ala Asn Gly Ile Lys Ile Gly Pro Gln His Ala
 180 185 190

 gct acc aat gca tct cac gga ggc aac caa gga ggg cag cag gca ggg 624
 Ala Thr Asn Ala Ser His Gly Gly Asn Gln Gly Gly Gln Gln Ala Gly
 195 200 205

 gga ggc tgc tgc tga 639
 Gly Gly Cys Cys
 210

<210> 67
 <211> 212
 <212> PRT
 <213> Rattus sp.

<400> 67
 Met Ala Tyr Ala Tyr Leu Phe Lys Tyr Ile Ile Ile Gly Asp Thr Gly
 1 5 10 15

 Val Gly Lys Ser Cys Leu Leu Leu Gln Phe Thr Asp Lys Arg Phe Gln
 20 25 30

 Pro Val His Asp Leu Thr Ile Gly Val Glu Phe Gly Ala Arg Met Ile
 35 40 45

 Thr Ile Asp Gly Lys Gln Ile Lys Leu Gln Ile Trp Asp Thr Ala Gly
 50 55 60

 Gln Glu Ser Phe Arg Ser Ile Thr Arg Ser Tyr Tyr Arg Gly Ala Ala
 65 70 75 80

 Gly Ala Leu Leu Val Tyr Asp Ile Thr Arg Arg Asp Thr Phe Asn His
 85 90 95

 Leu Thr Thr Trp Leu Glu Asp Ala Arg Gln His Ser Asn Ser Asn Met
 100 105 110

 Val Ile Met Leu Ile Gly Asn Lys Ser Asp Leu Glu Ser Arg Arg Glu
 115 120 125

 Val Lys Lys Glu Glu Gly Glu Ala Phe Ala Arg Glu His Gly Leu Ile
 130 135 140

 Phe Met Glu Thr Ser Ala Lys Thr Ala Ser Asn Val Glu Glu Ala Phe
 145 150 155 160

 Ile Asn Thr Ala Lys Glu Ile Tyr Glu Lys Ile Gln Glu Gly Val Phe
 165 170 175

00670756.062700

Asp Ile Asn Asn Glu Ala Asn Gly Ile Lys Ile Gly Pro Gln His Ala
180 185 190

Ala Thr Asn Ala Ser His Gly Gly Asn Gln Gly Gly Gln Gln Ala Gly
195 200 205

Gly Gly Cys Cys
210

<210> 68

<211> 816

<212> DNA

<213> Rattus sp.

<220>

<221> CDS

<222> (1)..(813)

<400> 68

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gag tat caa gtg ggg cag ctg tac tct gtg gct gaa gcc agt aaa aat 96
Glu Tyr Gln Val Gly Gln Leu Tyr Ser Val Ala Glu Ala Ser Lys Asn
20 25 30

gaa act ggt ggt ggg gaa ggt gtg gag gtc ctg gtg aac gag ccc tac 144
Glu Thr Gly Gly Gly Glu Gly Val Glu Val Leu Val Asn Glu Pro Tyr
35 40 45

gag aag gat gat ggc gag aaa ggc cag tac aca cac aag atc tac cac 192
Glu Lys Asp Asp Gly Glu Lys Gly Gln Tyr Thr His Lys Ile Tyr His
50 55 60

tta cag agc aaa gtt ccc acg ttt gtt cga atg ctg gcc cca gaa ggc 240
Leu Gln Ser Lys Val Pro Thr Phe Val Arg Met Leu Ala Pro Glu Gly
65 70 75 80

gcc ctg aat ata cat gag aaa gcc tgg aat gcc tac cct tac tgc aga 288
Ala Leu Asn Ile His Glu Lys Ala Trp Asn Ala Tyr Pro Tyr Cys Arg
85 90 95

acc gtt att aca aat gag tac atg aag gaa gac ttt ctc att aaa att 336
Thr Val Ile Thr Asn Glu Tyr Met Lys Glu Asp Phe Leu Ile Lys Ile
100 105 110

gaa acc tgg cac aag cca gac ctt ggc acc cag gag aat gtg cat aaa 384
Glu Thr Trp His Lys Pro Asp Leu Gly Thr Gln Glu Asn Val His Lys
115 120 125

ctg gag cct gag gca tgg aaa cat gtg gaa gct ata tat ata gac atc 432
Leu Glu Pro Glu Ala Trp Lys His Val Glu Ala Ile Tyr Ile Asp Ile
130 135 140

gct gat cga agc caa gta ctt agc aag gat tac aag gca gag gaa gac 480
Ala Asp Arg Ser Gln Val Leu Ser Lys Asp Tyr Lys Ala Glu Glu Asp
145 150 155 160

cca gca aaa ttt aaa tct atc aaa aca gga cga gga cca ttg ggc ccg 528

00260055266

Pro Ala Lys Phe Lys Ser Ile Lys Thr Gly Arg Gly Pro Leu Gly Pro
 165 170 175

aat tgg aag caa gaa ctt gtc aat cag aag gac tgc cca tat atg tgt 576
 Asn Trp Lys Gln Glu Leu Val Asn Gln Lys Asp Cys Pro Tyr Met Cys
 180 185 190

gca tac aaa ctg gtt act gtc aag ttc aag tgg tgg ggc ttg cag aac 624
 Ala Tyr Lys Leu Val Thr Val Lys Phe Lys Trp Trp Gly Leu Gln Asn
 195 200 205

aaa gtg gaa aac ttt ata cat aag caa gag aag cgt ctg ttt aca aac 672
 Lys Val Glu Asn Phe Ile His Lys Gln Glu Lys Arg Leu Phe Thr Asn
 210 215 220

ttt cac agg cag ctg ttc tgt tgg ctt gat aaa tgg gtt gat ctg act 720
 Phe His Arg Gln Leu Phe Cys Trp Leu Asp Lys Trp Val Asp Leu Thr
 225 230 235 240

atg gat gac att cgg agg atg gaa gaa gag acg aag aga cag ctg gat 768
 Met Asp Asp Ile Arg Arg Met Glu Glu Thr Lys Arg Gln Leu Asp
 245 250 255

gag atg aga caa aag gac ccc gtg aaa gga atg aca gca gat gac tag 816
 Glu Met Arg Gln Lys Asp Pro Val Lys Gly Met Thr Ala Asp Asp
 260 265 270

<210> 69

<211> 2263

<212> DNA

<213> Simian sp.

<400> 69

cgctctctc ctcccccttc tctagcagta gccttctttaa tgtagttaa tggctttaca 60

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catgaacttg gaagggttg aaatgatagc agttctgac gtcattgtgc tttttgttaa 180

attatttgaa cagtttgggc tgattgaagc aggttttagaa gacagcgtgg aagatgaact 240

ggagatggcc actgtcaggc atcggcctga ggccttgag cttctggaag cccagagcaa 300

atttaccag aaagagcttc agatccttta cagaggattt aagaacgaat gccccagtgg 360

tggtgttaat gaagaaacct tcaaagagat ttactcgacg tcttttccac agggagactc 420

tacaacatat gcacattttc tgttcaatgc gtttgatacg gaccacaatg gagctgtgag 480

tttcaggatg ttcacaaag gtctttccat tttgctccgg gggcagtagc aagaaaaact 540

caattgggca tttaatctgt atgatataaa taaagatggc tacatcacta aagaggaaat 600

gottgatata atgaaagcaa tatacgacat gatgggtaaa tgtacatatc ctgtctctcaa 660

agaagatgca cccagacaac acgtcgaaac attttttcag aaaatggaca aaaataaaga 720

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 tttggatttg tttaatctta caggctgttt tccattgtat catcaagtgg aagtccaaga 1560
 cggcatcaaa caaaacaagg atgtttacag acatatgcaa agggtcagga tatctatcct 1620
 ccagtatatg ttaatgttta ataacaagta atcctaacag cattaaggcg caaatctgtc 1680
 ctctttcccc tgacttcctt acagcatgtt tatattacaa gccattcagg gacaaagaaa 1740
 ccttgactac ccactgtct actaggaaca aacaaacagc aagcaaaatt cactttgaaa 1800
 gcaccagtgg ttccattaca ttgacaacta ctaccaagat tcagttagaaa ataagtgtct 1860
 aacaactaat ccagattaca atatgattta gtgcatcata aaattccaac aattcagatt 1920
 atttttaate acctcagcca caactgtaaa gttgccacat tactaaagac acacacatcg 1980
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 ccctgctatc accagtgtag aaattaagag tagtacaata catgtacact gaaatttgcc 2160
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 caaaataaaa tgtttataac tctaaaaaaa aaaaaaaaaa aaa 2263

<210> 70

<211> 229

<212> PRT

<213> Simian sp.

<400> 70

Met Asn Leu Glu Gly Leu Glu Met Ile Ala Val Leu Ile Val Ile Val

1

5

10

15

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agtggTgttg ttaatgaaga aaccttcaaa gagatttact cgcagttctt tccacaggga 420
gactctacaa catatgcaca ttttctgttc aatgcgtttg atacggacca caatggagct 480
gtgagtttgc aggatttcat caaaggctct tccattttgc tccgggggac agtacaagaa 540
aaactcaatt gggcatttaa tctgtatgat ataaataaag atggctacat cactaaagag 600
gaaatgcttg atataatgaa agcaatatac gacatgatgg gtaaagtac atatcctgtc 660
ctcaagaag atgcacccag acaacacgtc gaaacatttt ttcagaaaat ggacaaaaat 720
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 aaaaacaaaa taaaatgtta aaaaaaaaaa aaaaaaaaaa 2259

<210> 72
 <211> 250
 <212> PRT
 <213> Simian sp.

<400> 72
 Met Asn Val Arg Arg Val Glu Ser Ile Ser Ala Gln Leu Glu Glu Ala
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 Ser Ser Thr Gly Gly Phe Leu Tyr Ala Gln Asn Ser Thr Lys Arg Ser
 20 25 30
 Ile Lys Glu Arg Leu Met Lys Leu Leu Pro Cys Ser Ala Ala Lys Thr
 35 40 45
 Ser Ser Pro Ala Ile Gln Asn Ser Val Glu Asp Glu Leu Glu Met Ala
 50 55 60
 Thr Val Arg His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser
 65 70 75 80
 Lys Phe Thr Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn
 85 90 95
 Glu Cys Pro Ser Gly Val Val Asn Glu Thr Phe Lys Glu Ile Tyr
 100 105 110
 Ser Gln Phe Phe Pro Gln Gly Asp Ser Thr Thr Tyr Ala His Phe Leu
 115 120 125
 Phe Asn Ala Phe Asp Thr Asp His Asn Gly Ala Val Ser Phe Glu Asp
 130 135 140
 Phe Ile Lys Gly Leu Ser Ile Leu Leu Arg Gly Thr Val Gln Glu Lys
 145 150 155 160
 Leu Asn Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile
 165 170 175
 Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ala Ile Tyr Asp Met Met
 180 185 190
 Gly Lys Cys Thr Tyr Pro Val Leu Lys Glu Asp Ala Pro Arg Gln His
 195 200 205
 Val Glu Thr Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Val Val
 210 215 220
 Thr Ile Asp Glu Phe Ile Glu Ser Cys Gln Lys Asp Glu Asn Ile Met
 225 230 235 240
 Arg Ser Met Gln Leu Phe Glu Asn Val Ile
 245 250

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<210> 73
<211> 10
<212> PRT
<213> Simian sp.

<400> 73
Ser Asn Ala Lys Ala Val Glu Thr Asp Val
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